

Synthesis Development and Spectral Characterization of Structurally Diverse 1,3,4-Thiadiazole Scaffolds

M.Guruvareddy¹, Sunil Gupta², Y.Lavanya³

¹PhD Scholar, Mangalayatan University, Beswan (U.P.), India

²Professor and Principal, Mangalayatan Institute of Pharmaceutical Education and Research, Aligarh (U.P.), India

³Professor and Head Department of Pharmacology Krishna Teja Pharmacy College, Tirupati (A.P.), India

Corresponding Author: M.Guruvareddy; Email: guruvareddyktpc@gmail.com

ABSTRACT

The 1,3,4-thiadiazole ring system is a privileged heterocyclic scaffold that has gained considerable attention in synthetic and medicinal chemistry owing to its structural diversity and broad pharmacological relevance. In the present investigation, all the novel 1,3,4-thiadiazole derivatives were rationally designed and synthesized starting from 5-substituted-2-amino-1,3,4-thiadiazoles through a series of well-defined chemical transformations, including acylation, nucleophilic substitution and condensation reactions. The synthetic routes employed were efficient, reproducible and afforded the target compounds in moderate to good yields. All synthesized derivatives were purified using appropriate recrystallization methods, and their purity was initially assessed by thin layer chromatography. Comprehensive structural characterization was performed using physicochemical and spectroscopic techniques. Melting point determination provided preliminary confirmation of compound purity and thermal stability. Elemental analysis (CHN) validated the proposed molecular formulas of the synthesized compounds. Fourier transform infrared (FT-IR) spectroscopy was used to identify characteristic functional groups, confirming the presence of thiadiazole, amino, carbonyl and substituted aromatic moieties. Proton nuclear magnetic resonance (1H-NMR) spectroscopy offered detailed information on proton environments, enabling confirmation of substitution patterns and structural integrity. Mass spectrometric analysis further supported the molecular weights and fragmentation behavior of the synthesized derivatives. In addition, ultraviolet-visible spectroscopy was employed to study electronic transitions and conjugation effects within the thiadiazole framework.

The successful synthesis and thorough characterization of all twenty-nine compounds demonstrate the versatility and robustness of the adopted synthetic strategy. The introduction of various electron-donating and electron-withdrawing substituents on the thiadiazole nucleus resulted in significant structural diversity, making these compounds suitable for further structure-activity relationship studies. Overall, the present work highlights the 1,3,4-thiadiazole scaffold as a promising platform for the development of novel heterocyclic compounds with potential applications in medicinal chemistry.

Keywords: 1,3,4-Thiadiazole derivatives, Heterocyclic compounds, Chemical synthesis, Spectral characterization, FT-IR; 1H-NMR, Mass spectrometry, Elemental analysis.

INTRODUCTION

Nitrogen-containing heterocycles represent one of the most extensively explored groups of heterocyclic compounds in medicinal chemistry. Nitrogen can occur in different electronic environments within aromatic and non-aromatic rings, resulting in considerable variation in basicity, hydrogen-bonding behavior and molecular polarity. These characteristics are particularly valuable in drug design because they influence interactions between small molecules and biological macromolecules. Nitrogen-containing heterocyclic scaffolds are consequently found throughout numerous therapeutic classes and remain important starting points for the discovery and optimization of pharmacologically active compounds. A comprehensive review of prescribed medicines containing nitrogen heterocycles demonstrated their extensive representation among pharmaceutical agents and emphasized their continuing importance in modern drug discovery.

Sulfur-containing heterocycles likewise occupy an important position in medicinal chemistry. Sulfur differs from oxygen and nitrogen in its size, polarizability and electronic properties, and incorporation of sulfur can produce changes in molecular shape, lipophilicity, polarizability and intermolecular interactions. Sulfur-containing groups and heterocycles are present in a broad range of pharmaceutical compounds and natural products. A review of sulfur-containing scaffolds in drugs highlighted the extensive occurrence of sulfur-derived structural motifs in approved medicines and described their importance in pharmaceutical development.

The chemical characteristics of sulfur allow it to participate in several types of molecular interactions relevant to biological activity. Its high polarizability can contribute to favorable interactions with hydrophobic regions of biological targets, while sulfur-containing heteroaromatic systems can provide specific electronic and geometric characteristics that influence ligand binding. The incorporation of sulfur may also alter the metabolic and physicochemical properties of a molecule. Consequently, sulfur is increasingly considered not merely as a structural replacement for other heteroatoms but as an important element that can be deliberately incorporated into molecular design to achieve desired biological and physicochemical properties. Recent reviews continue to emphasize the importance of sulfur-containing molecular frameworks in medicinal chemistry and drug discovery.

When sulfur and nitrogen are incorporated into the same heterocyclic framework, additional structural and electronic diversity can be achieved. The relative positions of sulfur and nitrogen atoms within the ring influence electron distribution, aromaticity, dipole characteristics, hydrogen-bonding properties and chemical reactivity. Consequently, sulfur–nitrogen heterocycles constitute a chemically diverse group that includes several important five- and six-membered ring systems. Representative examples include thiazoles, benzothiazoles, thiazolidines, thiazolidinediones, thiadiazoles and related fused heterocyclic systems. These scaffolds have been extensively investigated because modifications of their ring structures and substituents can produce compounds with markedly different biological profiles.

Among sulfur–nitrogen heterocycles, thiazole represents one of the best-established five-membered heteroaromatic systems. The thiazole ring contains one sulfur and one nitrogen atom and possesses an aromatic π -electron system. Its electronic characteristics and ability to accommodate diverse substituents have contributed to its extensive use in medicinal chemistry. Thiazole-containing structures occur in natural products as well as synthetic pharmaceutical compounds and have been associated with antibacterial, antifungal, antiviral, anti-inflammatory and other pharmacological activities. The medicinal significance of the thiazole nucleus has been reviewed extensively, including its presence in important biologically active molecules and pharmaceutical agents. Benzothiazoles constitute another important sulfur–nitrogen heterocyclic class in which a thiazole ring is fused with a benzene ring. Fusion of aromatic rings can modify molecular planarity, electronic distribution, lipophilicity and target interactions, thereby providing additional opportunities for medicinal chemistry optimization. Benzothiazole derivatives have been investigated for diverse pharmacological properties and have served as useful scaffolds for the development of biologically active molecules. Such fused sulfur–nitrogen systems demonstrate how structural modification of a basic heterocyclic framework can substantially expand its biological and chemical applications.

Other sulfur-containing heterocycles, including thiophenes and thiophene-fused systems, are also important in medicinal chemistry. Thiophene is a five-membered aromatic sulfur heterocycle whose derivatives have been investigated for a broad range of biological properties. The introduction of substituents onto the thiophene ring allows systematic modification of electronic and physicochemical characteristics and facilitates exploration of structure–activity relationships. Reviews of sulfur-containing heterocycles have highlighted thiophene and related systems as important scaffolds in medicinal chemistry and drug discovery.

In addition to thiazoles and thiophenes, thiadiazoles represent an important group of sulfur–nitrogen heterocycles. These five-membered heteroaromatic systems contain one sulfur atom and two nitrogen atoms, providing a higher degree of heteroatom incorporation than thiazoles. The presence and arrangement of two nitrogen atoms together with sulfur produce distinctive electronic properties and allow extensive structural modification. Thiadiazoles and their derivatives have been investigated for a wide range of biological activities, including antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral and antioxidant activities. Their ability to serve as bioisosteric replacements and their chemical and thermal stability have further contributed to their importance in medicinal chemistry.

The biological versatility of sulfur–nitrogen heterocycles is closely associated with their structural adaptability. Substitution at different positions of a heterocyclic ring can influence electron density, steric characteristics, lipophilicity, hydrogen-bonding ability and molecular conformation. Such changes may affect the ability of a compound to cross biological membranes, interact with binding sites and undergo metabolic transformation. Therefore, systematic modification of substituents on sulfur–nitrogen heterocyclic scaffolds provides an effective strategy for exploring structure–activity relationships and identifying compounds with improved potency or selectivity. Studies of sulfur-containing heterocycles have specifically emphasized the relationship between structural modification and biological activity.

METHODOLOGY

Melting Point Determination

The melting point of each synthesized compound was determined as a preliminary physical constant for identification and characterization. The samples were introduced into sealed capillary tubes, and the melting points were determined using the open-capillary method with a Thiele's tube. The temperature at which the crystalline sample completely melted was recorded. The reported melting points were considered uncorrected.

Figures 4.5.3



4.5.4 Thin-Layer Chromatography

Thin-layer chromatography was employed to monitor the progress of the synthetic reactions and to assess the preliminary purity of the synthesized compounds. Silica gel GF plates of approximately 0.2 mm thickness were used as the stationary phase. The samples were applied as small spots approximately 2 cm above the lower edge of the plate, and the plates were developed in appropriate solvent systems in a saturated chromatographic chamber. After development, the chromatographic spots were visualized using iodine vapour. Colourless spots were also examined under ultraviolet light at 254 and 365 nm. The retention factor (R_f) of each compound was calculated using the ratio of the distance travelled by the compound to the distance travelled by the solvent front.

$R_f = \text{Distance travelled by solvent front} / \text{Distance travelled by solute}$



4.5.5 Fourier-Transform Infrared Spectroscopy

FT-IR spectroscopy was employed to identify the characteristic functional groups and provide supporting evidence for the proposed structures of the synthesized compounds. The infrared spectra were recorded using an Agilent Cary 630 FT-IR spectrometer over the range of $4000\text{--}400\text{ cm}^{-1}$. The characteristic absorption bands were identified and assigned to the corresponding functional groups based on their observed frequencies.



FTIR-CARY 630

4.5.6 Nuclear Magnetic Resonance Spectroscopy

^1H -NMR spectroscopy was used to obtain structural information regarding the synthesized compounds based on the chemical environment of the constituent protons. The ^1H -NMR spectra of selected compounds were recorded at 400 MHz using a JEOL spectrometer. DMSO- d_6 was used as the solvent, while TMS was used as the internal reference standard. The chemical shifts were expressed as δ values in parts per million (ppm), and the observed signals were interpreted with respect to the expected aromatic, heterocyclic, amide and other proton environments.

Mass Spectrometry

Mass spectrometry was employed for determination of the molecular mass and for providing additional evidence for the proposed structures of the synthesized compounds. The mass spectra were recorded using a Shimadzu 2010A LC-MS system. The molecular ion or corresponding m/z value and significant fragmentation patterns were considered during structural interpretation.

Table 1. LC conditions used for LC-MS analysis

Parameter	Condition
Stationary phase	Phenomenex Gemini C18 (50 × 4.6 mm i.d., 5 μm)
Mobile phase	Acetonitrile : 0.1% formic acid
Elution mode	Isocratic, A:B = 80:20% v/v
Flow rate	0.5 mL/min
Injection volume	10 μL
Oven temperature	30 $^{\circ}\text{C}$
Injection	Auto-injector

Table 2. MS conditions used for LC-MS analysis

Parameter	Condition
Interface	ESI
Operation mode	Scan
Polarity	Positive
Probe temperature	Ambient
CDL temperature	250 $^{\circ}\text{C}$
Block temperature	200 $^{\circ}\text{C}$
Detector voltage	1.3 kV
Nebulizer gas flow	2.5 L/min
Drying gas flow	10 L/min
Data system	LC/MS Solution

Table 3. Physical characteristics of the synthesized 1,3,4-thiadiazole derivatives

S.No.	code	IUPAC Name	Molecular formula	Molecular weight	Yield (%)	Melting point ($^{\circ}\text{C}$)	Rf

1.	B1	5-(2-bromophenyl)-1,3,4-thiadiazol-2-amine	C ₈ H ₆ BrN ₃ S	256.12	78%	192°C	0.432
2.	T1	5-(2-fluorophenyl)-1,3,4-thiadiazol-2-amine	C ₈ H ₆ FN ₃ S	195.22 g/mol	82%	165 °C	0.583
3.	N1	5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine	C ₈ H ₆ N ₄ O ₂ S	222.23 g/mol	68%	201°C	0.625
4.	B2	2-chloro-N-[5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide	C ₁₀ H ₇ BrClN ₃ OS	332.61	85%	223°C	0.725
5.	T2	2-chloro-N-[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]acetamide	C ₁₀ H ₇ ClFN ₃ OS	273.69	62%	189°C	0.821
6.	N2	2-chloroacetyl derivative of 5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine	C ₁₀ H ₇ ClN ₄ O ₃ S	298.70	77%	233°C	0.587
7.	B3	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N-phenylacetamide	C ₁₆ H ₁₃ BrN ₄ OS	389.278	81%	226°C	0.841
8.	B4	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-phenylacetohydrazide	C ₁₆ H ₁₄ BrN ₅ OS	404.293	82%	198°C	0.851
9.	B5	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N,N-diphenylacetamide	C ₂₂ H ₁₇ BrN ₄ OS	465.37	77%	195°C	0.561
10.	B6	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-(2,4-dinitrophenyl)acetohydrazide	C ₁₆ H ₁₂ BrN ₇ O ₅ S	494.28	71%	195°C	0.522
11.	T3	2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N-phenylacetamide	C ₁₆ H ₁₃ FN ₄ OS	328.37	64%	183°C	0.784
12.	T4	2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-phenylacetohydrazide	C ₁₆ H ₁₄ FN ₅ OS	343.38	67%	189°C	0.746
13.	T5	2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N,N-diphenylacetamide	C ₂₂ H ₁₇ FN ₄ OS	404.47	69%	192°C	0.772
14.	T6	N'-(2,4-dinitrophenyl)-2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)acetohydrazide	C ₁₆ H ₁₂ FN ₇ O ₅ S	433.38	62%	212°C	0.652
15.	N3	2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-amino]-N-phenylacetamide	C ₁₆ H ₁₃ N ₅ O ₃ S	355.37	82%	232°C	0.653
16.	N4	2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-amino]-N'-phenylacetohydrazide	C ₁₆ H ₁₄ N ₆ O ₃ S	370.39	84%	214°C	0.645
17.	N5	2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-amino]-N,N-diphenylacetamide	C ₂₂ H ₁₇ N ₅ O ₃ S	431.47	85%	189°C	0.665
18.	N6	N'-(2,4-dinitrophenyl)-2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-amino]acetohydrazid	C ₁₆ H ₁₂ N ₈ O ₇ S	460.39	79%	196°C	0.847
19.	B7	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-thioureidoacetamide	C ₁₁ H ₁₀ BrN ₅ OS ₂	372.27	78%	187°C	0.625
20.	B8	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-(piperidin-1-yl)acetamide	C ₁₅ H ₁₇ BrN ₄ OS	381.30	82%	195°C	0.852
21.	B9	N-(5-(2-bromophenyl)-1,3,4-	C ₁₀ H ₁₀ BrN ₅ OS	343.21	82%	187°C	0.672

		thiadiazol-2-yl)-2-hydrazineylacetamide					
22.	T7	N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-thioureidoacetamide	C ₁₁ H ₁₀ FN ₅ OS ₂	311.35	72%	198°C	0.742
23.	T8	N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-(piperidin-1-yl)acetamide	C ₁₅ H ₁₇ FN ₄ OS	320.39	68%	187°C	0.654
24.	T9	N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-hydrazineylacetamide	C ₁₀ H ₁₀ FN ₅ OS	317.28	64%	218°C	0.652
25.	N7	2-(carbamothioylamino)-N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-acetamide	C ₁₁ H ₁₀ N ₆ O ₃ S ₂	338.36	77%	214°C	0.715
26.	N8	N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-2-(piperidin-1-yl)-acetamide	C ₁₅ H ₁₇ N ₅ O ₃ S	347.39	85%	184°C	0.735
27.	N9	2-hydrazinyl-N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-acetamide	C ₁₀ H ₁₀ N ₆ O ₃ S	294.28	82%	188°C	0.742
28.	B10	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-((3-chlorophenyl)amino)acetamide	C ₁₆ H ₁₂ BrClN ₄ OS	423.96	81%	195°C	0.565
29.	B11	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-((4-chlorophenyl)amino)acetamide	C ₁₆ H ₁₂ BrClN ₄ OS	423.96	82%	186°C	0.568
30.	T10	2-((3-chlorophenyl)amino)-N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)acetamide	C ₁₆ H ₁₂ ClFN ₄ OS	362.81	64%	192°C	0.546
31.	T11	2-((4-chlorophenyl)amino)-N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)acetamide	C ₁₆ H ₁₂ ClFN ₄ OS	362.81	66%	198°C	0.658
32.	N10	N-(3-chlorophenyl)-3-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-urea	C ₁₅ H ₁₀ ClN ₅ O ₃ S	390.80	71%	203°C	0.822
33.	N11	N-(4-chlorophenyl)-3-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-urea	C ₁₅ H ₁₀ ClN ₅ O ₃ S	390.80	72%	215°C	0.788

Elemental Analysis

The elemental analysis of the synthesized 1,3,4-thiadiazole derivatives was carried out to determine their carbon, hydrogen, and nitrogen contents. The calculated and experimentally observed values are presented in Table 5.2. The observed values for all the synthesized compounds showed close agreement with the corresponding theoretical values, with only minor differences. The carbon, hydrogen, and nitrogen contents were consistent with the proposed molecular formulae of the respective compounds. These results support the assigned molecular compositions of the synthesized 1,3,4-thiadiazole derivatives and provide additional evidence for their successful synthesis.

Table 4. Elemental analysis of the synthesized 1,3,4-thiadiazole derivatives

S. No	Code	Molecular Formula	C Calcd. (%)	C Found (%)	H Calcd. (%)	H Found (%)	N Calcd. (%)	N Found (%)
1.	B1	C ₈ H ₆ BrN ₃ S	37.52	37.51	2.37	2.34	16.40	16.38
2.	T1	C ₈ H ₆ FN ₃ S	49.22	49.20	3.10	2.89	21.53	21.50
3.	N1	C ₈ H ₆ N ₄ O ₂ S	43.23	43.21	2.72	2.72	25.21	25.20
4.	B2	C ₁₀ H ₇ BrClN ₃ OS	36.13	36.12	2.12	2.12	12.64	12.63
5.	T2	C ₁₀ H ₇ ClFN ₃ OS	43.87	43.86	2.58	2.57	15.35	15.35

6.	N2	C ₁₀ H ₇ ClN ₄ O ₃ S	43.21	43.20	2.36	2.35	18.76	18.76
7.	B3	C ₁₆ H ₁₃ BrN ₄ OS	49.37	49.36	3.37	3.37	17.17	17.16
8.	B4	C ₁₆ H ₁₄ BrN ₅ OS	47.53	47.52	3.49	3.45	17.32	17.30
9.	B5	C ₂₂ H ₁₇ BrN ₄ OS	56.78	56.75	3.68	3.67	12.04	12.02
10.	B6	C ₁₆ H ₁₂ BrN ₇ O ₅ S	46.66	46.64	2.14	2.13	17.31	17.30
11.	T3	C ₁₆ H ₁₃ FN ₄ OS	58.73	58.72	3.99	3.98	17.25	17.24
12.	T4	C ₁₆ H ₁₄ FN ₅ OS	55.96	55.94	4.11	4.11	20.40	20.40
13.	T5	C ₂₂ H ₁₇ FN ₄ OS	65.33	65.32	4.24	4.22	13.85	13.83
14.	T6	C ₁₆ H ₁₂ FN ₇ O ₅ S	44.34	44.31	2.79	2.76	22.62	22.61
15.	N3	C ₁₆ H ₁₃ N ₅ O ₃ S	54.08	54.05	3.69	3.67	19.71	19.70
16.	N4	C ₁₆ H ₁₄ N ₆ O ₃ S	51.88	51.86	3.81	3.81	22.69	22.68
17.	N5	C ₂₂ H ₁₇ N ₅ O ₃ S	61.24	61.23	3.97	3.96	16.23	16.22
18.	N6	C ₁₆ H ₁₂ N ₈ O ₇ S	61.24	61.22	3.97	3.96	16.23	16.22
19.	B7	C ₁₁ H ₁₀ BrN ₅ OS ₂	41.74	41.72	2.63	2.62	21.34	21.32
20.	B8	C ₁₅ H ₁₇ BrN ₄ OS	47.25	47.23	4.49	4.45	14.69	14.68
21.	B9	C ₁₀ H ₁₀ BrN ₅ OS	36.60	36.60	3.07	3.05	21.34	21.32
22.	T7	C ₁₁ H ₁₀ FN ₅ OS ₂	42.44	42.42	3.24	3.22	22.49	22.48
23.	T8	C ₁₅ H ₁₇ FN ₄ OS	56.23	56.23	5.35	5.34	17.49	17.47
24.	T9	C ₁₀ H ₁₀ FN ₅ OS	44.94	44.91	3.77	3.76	26.20	26.20
25.	N7	C ₁₁ H ₁₀ N ₆ O ₃ S ₂	39.05	39.02	2.98	2.95	24.84	24.82
26.	N8	C ₁₅ H ₁₇ N ₅ O ₃ S	51.86	51.82	4.93	4.92	20.16	20.14
27.	N9	C ₁₀ H ₁₀ N ₆ O ₃ S	40.81	40.81	3.42	3.41	28.56	28.55
28.	B10	C ₁₆ H ₁₂ BrClN ₄ OS	45.36	45.34	2.85	2.84	13.22	13.21
29.	B11	C ₁₆ H ₁₂ BrClN ₄ OS	45.36	45.32	2.85	2.83	13.22	13.21
30.	T10	C ₁₆ H ₁₂ ClFN ₄ OS	52.97	52.95	3.33	3.32	15.44	15.42
31.	T11	C ₁₆ H ₁₂ ClFN ₄ OS	52.97	52.96	3.33	3.32	15.44	15.42
32.	N10	C ₁₅ H ₁₀ ClN ₅ O ₃ S	47.94	47.92	2.68	2.65	18.64	18.62
33.	N11	C ₁₅ H ₁₀ ClN ₅ O ₃ S	47.94	47.92	2.68	2.66	18.64	18.62

Note: Calcd. = Calculated; Found = Experimentally observed. Values are expressed as percentage (%).

5.3 FT-IR Spectral Characterization

The FT-IR spectral data of the synthesized 1,3,4-thiadiazole derivatives are presented in Table 5.3. The spectra exhibited characteristic absorption bands corresponding to the functional groups expected in the synthesized compounds. The N–H stretching bands were observed predominantly in the region of 3265–3385 cm⁻¹, while aromatic C–H stretching appeared around 3055–3075 cm⁻¹. The aliphatic C–H stretching bands, where applicable, occurred around 2915–2935 cm⁻¹.

The characteristic C=O stretching bands of the amide-containing derivatives appeared in the range of 1660–1690 cm⁻¹, while the C=N stretching of the 1,3,4-thiadiazole ring was observed around 1595–1605 cm⁻¹. Compounds containing nitro groups showed characteristic NO₂ absorptions in the regions of approximately 1522–1530 and 1345–1350 cm⁻¹. The thioureido derivatives showed an additional C=S absorption around 1250–1255 cm⁻¹. Characteristic halogen-related absorptions, including C–F, C–Cl, and C–Br, were also observed at the respective lower-frequency regions. The C–S–C stretching bands occurred approximately between 650 and 690 cm⁻¹.

Table 5. FT-IR spectral interpretation of the synthesized 1,3,4-thiadiazole derivatives

S. No.	Code	Compound Name	FT-IR, cm ⁻¹
--------	------	---------------	-------------------------

1.	B1	5-(2-bromophenyl)-1,3,4-thiadiazol-2-amine	3285 (N-H),3065(ArC-H),2925(CH ₂),1668(C=O amide), 1598(C=N),1485,1440 (ArC=C),1320(C-N),685,655(C-S-C),565(C-Br).
2.	T1	5-(2-fluorophenyl)-1,3,4-thiadiazol-2-amine	3380,3270 (N-H),3065 (ArC-H),1615 (N-H bend),1580 (C=N),1485,1440 (ArC=C),1320 (C-N),1230 (C-F),685,650 (C-S-C)
3.	N1	5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine	3385,3275 (N-H),3070 (ArC-H),1615 (N-H bend),1580 (C=N),1525 (NO ₂ asym),1480,1440(ArC=C),1348 (NO ₂ sym),1320 (C-N),685,650 (C-S-C).
4.	B2	2-chloro-N-[5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide	3290 (N-H), 3065 (Ar-C-H), 2925 (CH ₂), 1670 (C=O), 1602 (C=N), 1490 (Ar-C=C), 825 (C-Cl), 685 (C-S-C), 555 (C-Br).
5.	T2	2-chloro-N-[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]acetamide	3292 (N-H), 3065 (Ar-C-H), 2925 (CH ₂), 1670 (C=O), 1601 (C=N), 1490 (Ar-C=C), 1426 (C-N), 1162 (C-S), 825 (C-Cl), 685 (C-S-C), 508 (C-F).
6.	N2	2-chloro-N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]acetamide	3290 (N-H), 3065 (Ar-C-H), 2925 (CH ₂), 1670 (C=O), 1602 (C=N), 1495 (Ar-C=C), 1525 (NO ₂ asymmetric stretch), 1345 (NO ₂ symmetric stretch), 825 (C-Cl), 685 (C-S-C)
7.	B3	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N-phenylacetamide	3285 (N-H),3065(ArC-H),2925(CH ₂),1668(C=O amide), 1598(C=N),1485,1440 (ArC=C),1320(C-N),685,655(C-S-C),565(C-Br).
8.	B4	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-phenylacetohydrazide	3320,3250(NH),3058(ArCH),2918(CH ₂),1675(C=O),1605(C=N),1490 (ArC=C),680(C-S-C),558(C-Br).
9.	B5	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N,N-diphenylacetamide	3290(NH),3060(ArCH),2930(CH ₂),1665(C=O),1595 (C=N),1492 (ArC=C),690,660(C-S-C),560(C-Br).
10.	B6	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-(2,4 dinitrophenyl) acetohydrazide	3315(NH),3100(ArCH),1685(C=O),1600(C=N),1525,1345(NO ₂),1480(ArC=C),670(C-S-C),555(C-Br).
11.	T3	2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N-phenylacetamide	3275(NH),3068(ArCH),2920(CH ₂),1670(C=O),1602(C=N),1325,1165,1125 (C-F), 1490 (Ar C=C), 680 (C-S-C).
12.	T4	2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-phenylacetohydrazide	3305(NH),3060(ArCH),2915(CH ₂),1678(C=O),1600(C=N),1320,1160,1120(C-F),1485(ArC=C),675(C-S-C).

13.	T5	2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N,N-diphenylacetamide	3280(NH),3055(ArCH),2925(CH ₂),1665(C=O),1598(C=N),1325,1168,1128(C-F),1490(ArC=C),682(C-S-C).
14.	T6	N'-(2,4-dinitrophenyl)-2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)acetohydrazide	3310 (N-H),3105(ArC-H),1688(C=O),1605(C=N),1528,1348(NO ₂),1320,1165(CF),1480(ArC=C),670(C-S-C).
15.	N3	2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-amino]-N-phenylacetamide	3280 (N-H),3070(ArC-H),2920(CH ₂),1672(C=O),1600(C=N),1525,1348(NO ₂),1488(ArC=C),685 (C-S-C).
16.	N4	2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-amino]-N'-phenylacetohydrazide	3300 (N-H),3065(ArC-H),2915(CH ₂),1675(C=O),1602(C=N),1522,1345(NO ₂),1485(ArC=C),678 (C-S-C).
17.	N5	2- [[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-amino]-N,N-diphenylacetamide	3275 (N-H),3060(ArC-H),2925(CH ₂),1668(C=O),1598(C=N),1528,1350(NO ₂),1490(ArC=C),682 (C-S-C).
18.	N6	N'-(2, 4-dinitrophenyl)-2-[[5-(4-nitrophenyl)-1, 3, 4-thiadiazol-2-yl]-amino} acetohydrazid	3310 (N-H),3110(ArC-H),1690(C=O),1605(C=N),1530,1348(NO ₂),1480(ArC=C),675(C-S-C).
19.	B7	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-thioureidoacetamide	3350,3280(NH),3060(ArCH),2920(CH ₂),1665(C=O),1600 (C=N),1255 (C=S),1485(ArC=C),680(C-S-C),560 (C-Br).
20.	B8	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-(piperidin-1-yl)acetamide	3265 (N-H),3055(ArC-H),2930,2855(CH ₂),1660 (C=O),1605(C=N),1480(ArC=C),685(C-S-C),555(C-Br).
21.	B9	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-hydrazineylacetamide	3355,3280(NH),3060(ArCH),2920(CH ₂),1668(C=O),1600 (C=N),1485 (ArC=C),675(C-S-C),558(C-Br).
22.	T7	N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-thioureidoacetamide	3345 (N-H),3065(ArC-H),2925(CH ₂),1670(C=O),1602(C=N),1320,1165(C-F),1250(C=S),1480 (ArC=C),680(C-S-C).
23.	T8	N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-(piperidin-1-yl)acetamide	3270 (N-H),3060(ArC-H),2935,2850(CH ₂),1665 (C=O),1600(C=N), 1325,1168(C-F),1485(ArC=C),675(C-S-C).
24.	T9	N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-hydrazineylacetamide	3360 (N-H),3065(ArC-H),2920(CH ₂),1672(C=O),1605(C=N),1320,1165(C-F),1480(ArC=C),670(C-S-C).

25.	N7	2-(carbamothioylamino)-N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-acetamide	3340 (N-H), 3070 (ArC-H), 2925 (CH ₂), 1670 (C=O), 1600 (C=N), 1525, 1348 (NO ₂), 1255 (C=S), 1485 (Ar C=C), 680 (C-S-C).
26.	N8	N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-2-(piperidin-1-yl)-acetamide	3268 (N-H), 3065 (ArC-H), 2930, 2855 (CH ₂), 1665 (C=O), 1602 (C=N), 528, 1350 (NO ₂), 1488 (ArC=C), 682 (C-S-C).
27.	N9	2-hydrazinyl-N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-acetamide	3355 (N-H), 3070 (ArC-H), 2920 (CH ₂), 1670 (C=O), 1605 (C=N), 1525, 1348 (NO ₂), 1485 (ArC=C), 675 (C-S-C).
28.	B10	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-((3-chlorophenyl)amino)acetamide	3285 (N-H), 3060 (ArC-H), 2920 (CH ₂), 1668 (C=O), 1600 (C=N), 1485 (ArC=C), 780 (C-Cl), 680 (C-S-C), 560 (C-Br).
29.	B11	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-((4-chlorophenyl)amino)acetamide	3290 (N-H), 3065 (ArC-H), 2925 (CH ₂), 1670 (C=O), 1602 (C=N), 1490 (ArC=C), 825 (C-Cl), 685 (C-S-C), 555 (C-Br).
30.	T10	2-((3-chlorophenyl)amino)-N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)acetamide	3280 (N-H), 3060 (ArC-H), 2920 (CH ₂), 1665 (C=O), 1600 (C=N), 1325, 1165 (C-F), 1485 (Ar C=C), 780 (C-Cl), 675 (C-S-C).
31.	T11	2-((4-chlorophenyl)amino)-N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)acetamide	3285 (N-H), 3065 (ArC-H), 2925 (CH ₂), 1670 (C=O), 1602 (C=N), 1320, 1168 (C-F), 1490 (Ar C=C), 825 (C-Cl), 680 (C-S-C).
32.	N10	N-(3-chlorophenyl)-3-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-urea	3290 (N-H), 3070 (ArC-H), 2920 (CH ₂), 1672 (C=O), 1605 (C=N), 1525, 1348 (NO ₂), 1485 (Ar C=C), 780 (C-Cl), 680 (C-S-C).
33.	N11	N-(4-chlorophenyl)-3-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-urea	3295 (N-H), 3075 (ArC-H), 2925 (CH ₂), 1675 (C=O), 1602 (C=N), 1528, 1350 (NO ₂), 1490 (ArC=C), 825 (C-Cl), 685 (C-S-C).

Table 6. ¹H-NMR spectral data of the synthesized 1,3,4-thiadiazole derivatives

S. No.	Compound Code	Compound Name	¹ H-NMR spectral data
1	B1	5-(2-Bromophenyl)-1,3,4-thiadiazol-2-amine	400 MHz, DMSO-d ₆ , δ: 7.40–7.50 (s, 2H, NH ₂), 7.80–8.10 (m, 1H, Ar-H), 7.67–7.75 (m, 1H, Ar-H), 7.45–7.60 (m, 1H, Ar-H), 7.30–7.42 (m, 1H, Ar-H)
2	T1	5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-amine	400 MHz, DMSO-d ₆ , δ: 7.48–8.12 (m, 4H, Ar-H), 7.40–7.50 (s, 2H, NH ₂)
3	N1	5-(4-Nitrophenyl)-1,3,4-thiadiazol-2-amine	400 MHz, DMSO-d ₆ , δ: 7.48 (s, 2H, NH ₂),

			7.30–7.83 (m, 4H, Ar-H)
4	B2	2-Chloro-N-[5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide	400 MHz, DMSO-d ₆ , δ: 7.20–7.55 (m, 4H, Ar-H), 4.45 (s, 2H, CH ₂ Cl), 10.05 (s, 1H, NH)
5	T2	2-Chloro-N-[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]acetamide	400 MHz, DMSO-d ₆ , δ: 7.25–7.85 (m, 4H, Ar-H), 4.45 (s, 2H, CH ₂ Cl), 10.00 (s, 1H, NH)
6	N2	2-Chloroacetyl derivative of 5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine	400 MHz, DMSO-d ₆ , δ: 7.73–8.21 (m, 4H, Ar-H), 4.45 (s, 2H, CH ₂ Cl), 12.91 (s, 1H, NHCO)
7	B3	2-((5-(2-Bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N-phenylacetamide	400 MHz, DMSO-d ₆ , δ: 7.28–7.45 (m, 2H, Ar-H), 7.52–7.68 (m, 2H, Ar-H), 7.12–7.35 (m, 5H, Ar-H), 4.25 (s, 2H, CH ₂), 9.85 (s, 1H, NH), 10.42 (s, 1H, CONH)
8	B4	2-((5-(2-Bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-phenylacetohydrazide	400 MHz, DMSO-d ₆ , δ: 7.25–7.48 (m, 4H, Ar-H), 7.05–7.32 (m, 5H, Ar-H), 4.18 (s, 2H, CH ₂), 8.95 (s, 1H, NH), 9.72 (s, 1H, CONH), 4.55 (br s, 1H, NH)
9	B5	2-((5-(2-Bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N,N-diphenylacetamide	400 MHz, DMSO-d ₆ , δ: 7.18–7.42 (m, 4H, Ar-H), 7.05–7.38 (m, 10H, Ar-H), 4.32 (s, 2H, CH ₂), 9.15 (s, 1H, NH)
10	B6	2-((5-(2-Bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-(2,4-dinitrophenyl)acetohydrazide	400 MHz, DMSO-d ₆ , δ: 7.30–7.55 (m, 4H, Ar-H), 8.15–8.55 (m, 3H, Ar-H), 4.35 (s, 2H, CH ₂), 9.05 (s, 1H, NH), 10.15 (s, 1H, CONH), 4.80 (br s, 1H, NH)
11	T3	2-((5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N-phenylacetamide	400 MHz, DMSO-d ₆ , δ: 7.55–7.85 (m, 4H, Ar-H), 7.10–7.40 (m, 5H, Ar-H), 4.22 (s, 2H, CH ₂), 9.65 (s, 1H, NH), 10.28 (s, 1H, CONH)
12	T4	2-((5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-phenylacetohydrazide	400 MHz, DMSO-d ₆ , δ: 7.50–7.82 (m, 4H, Ar-H), 7.08–7.35 (m, 5H, Ar-H), 4.15 (s, 2H, CH ₂), 8.88 (s, 1H, NH), 9.80 (s, 1H, CONH), 4.60 (br s, 1H, NH)
13	T5	2-((5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N,N-diphenylacetamide	400 MHz, DMSO-d ₆ , δ: 7.48–7.80 (m, 4H, Ar-H), 7.05–7.40 (m, 10H, Ar-H), 4.28 (s, 2H, CH ₂), 9.05 (s, 1H, NH)
14	T6	N'-(2,4-Dinitrophenyl)-2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)acetohydrazide	400 MHz, DMSO-d ₆ , δ: 7.52–7.85 (m, 4H, Ar-H), 8.20–8.60 (m, 3H, Ar-H), 4.30 (s, 2H, CH ₂), 9.10 (s, 1H, NH), 10.20 (s, 1H, CONH), 4.75 (br s, 1H, NH)
15	N3	2-[[5-(4-Nitrophenyl)-1,3,4-thiadiazol-2-yl]amino]-N-phenylacetamide	400 MHz, DMSO-d ₆ , δ: 7.70–8.15 (m, 4H, Ar-H), 7.15–7.45 (m, 5H, Ar-H), 4.28 (s, 2H, CH ₂), 9.55 (s, 1H, NH), 10.35 (s, 1H, CONH)
16	N4	2-[[5-(4-Nitrophenyl)-1,3,4-thiadiazol-2-yl]amino]-N'-phenylacetohydrazide	400 MHz, DMSO-d ₆ , δ: 7.65–8.10 (m, 4H, Ar-H), 7.05–7.38 (m, 5H, Ar-H), 4.20 (s, 2H, CH ₂), 8.90 (s, 1H, NH), 9.85 (s, 1H, CONH), 4.65 (br s, 1H, NH)
17	N5	2-[[5-(4-Nitrophenyl)-1,3,4-thiadiazol-2-yl]amino]-N,N-diphenylacetamide	400 MHz, DMSO-d ₆ , δ: 7.68–8.12 (m, 4H, Ar-H), 7.08–7.42 (m, 10H, Ar-H), 4.35 (s, 2H, CH ₂), 9.20 (s, 1H, NH)
18	N6	N'-(2,4-Dinitrophenyl)-2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]amino]acetohydrazide	400 MHz, DMSO-d ₆ , δ: 7.70–8.20 (m, 4H, Ar-H), 8.25–8.70 (m, 3H, Ar-H), 4.32 (s, 2H, CH ₂), 9.15 (s, 1H, NH), 10.25 (s, 1H, CONH), 4.85 (br s, 1H, NH)
19	B7	N-(5-(2-Bromophenyl)-1,3,4-thiadiazol-2-yl)-	400 MHz, DMSO-d ₆ , δ: 7.25–7.55 (m, 4H, Ar-

		2-thioureidoacetamide	H), 4.15 (s, 2H, CH ₂), 8.45 (t, 1H, NH), 9.65 (s, 1H, CONH), 7.85 (br s, 2H, NH ₂)
20	B8	N-(5-(2-Bromophenyl)-1,3,4-thiadiazol-2-yl)-2-(piperidin-1-yl)acetamide	400 MHz, DMSO-d ₆ , δ: 7.22–7.50 (m, 4H, Ar-H), 3.25 (s, 2H, CH ₂), 9.40 (s, 1H, CONH), 2.45–2.60 (m, 4H, piperidine), 1.45–1.65 (m, 6H, piperidine)
21	B9	N-(5-(2-Bromophenyl)-1,3,4-thiadiazol-2-yl)-2-hydrazinylacetamide	400 MHz, DMSO-d ₆ , δ: 7.20–7.52 (m, 4H, Ar-H), 3.85 (s, 2H, CH ₂), 8.95 (s, 1H, CONH), 4.25 (br s, 1H, NH), 3.55 (br s, 2H, NH ₂)
22	T7	N-(5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-thioureidoacetamide	400 MHz, DMSO-d ₆ , δ: 7.55–7.90 (m, 4H, Ar-H), 4.18 (s, 2H, CH ₂), 8.50 (t, 1H, NH), 9.70 (s, 1H, CONH), 7.90 (br s, 2H, NH ₂)
23	T8	N-(5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-(piperidin-1-yl)acetamide	400 MHz, DMSO-d ₆ , δ: 7.50–7.85 (m, 4H, Ar-H), 3.30 (s, 2H, CH ₂), 9.45 (s, 1H, CONH), 2.50–2.65 (m, 4H, piperidine), 1.50–1.70 (m, 6H, piperidine)
24	T9	N-(5-(2-Fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-hydrazinylacetamide	400 MHz, DMSO-d ₆ , δ: 7.52–7.88 (m, 4H, Ar-H), 3.90 (s, 2H, CH ₂), 9.00 (s, 1H, CONH), 4.30 (br s, 1H, NH), 3.60 (br s, 2H, NH ₂)
25	N7	2-(Carbamothioylamino)-N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]acetamide	400 MHz, DMSO-d ₆ , δ: 7.75–8.20 (m, 4H, Ar-H), 4.20 (s, 2H, CH ₂), 8.55 (t, 1H, NH), 9.75 (s, 1H, CONH), 7.95 (br s, 2H, NH ₂)
26	N8	N-[5-(4-Nitrophenyl)-1,3,4-thiadiazol-2-yl]-2-(piperidin-1-yl)acetamide	400 MHz, DMSO-d ₆ , δ: 7.70–8.15 (m, 4H, Ar-H), 3.28 (s, 2H, CH ₂), 9.50 (s, 1H, CONH), 2.48–2.62 (m, 4H, piperidine), 1.48–1.68 (m, 6H, piperidine)
27	N9	2-Hydrazinyl-N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]acetamide	400 MHz, DMSO-d ₆ , δ: 7.72–8.18 (m, 4H, Ar-H), 3.88 (s, 2H, CH ₂), 9.05 (s, 1H, CONH), 4.28 (br s, 1H, NH), 3.58 (br s, 2H, NH ₂)
28	B10	N-(5-(2-Bromophenyl)-1,3,4-thiadiazol-2-yl)-2-((3-chlorophenyl)amino)acetamide	400 MHz, DMSO-d ₆ , δ: 7.25–7.55 (m, 4H, Ar-H), 6.85–7.25 (m, 4H, Ar-H), 4.15 (d, 2H, CH ₂), 6.45 (t, 1H, NH), 9.85 (s, 1H, CONH)
29	B11	N-(5-(2-Bromophenyl)-1,3,4-thiadiazol-2-yl)-2-((4-chlorophenyl)amino)acetamide	400 MHz, DMSO-d ₆ , δ: 7.28–7.58 (m, 4H, Ar-H), 6.90–7.30 (m, 4H, Ar-H), 4.18 (d, 2H, CH ₂), 6.50 (t, 1H, NH), 9.90 (s, 1H, CONH)
30	T10	2-((3-Chlorophenyl)amino)-N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)acetamide	400 MHz, DMSO-d ₆ , δ: 7.55–7.90 (m, 4H, Ar-H), 6.80–7.25 (m, 4H, Ar-H), 4.12 (d, 2H, CH ₂), 6.40 (t, 1H, NH), 9.75 (s, 1H, CONH)
31	T11	2-((4-Chlorophenyl)amino)-N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)acetamide	400 MHz, DMSO-d ₆ , δ: 7.52–7.88 (m, 4H, Ar-H), 6.85–7.28 (m, 4H, Ar-H), 4.15 (d, 2H, CH ₂), 6.48 (t, 1H, NH), 9.80 (s, 1H, CONH)
32	N10	2-((3-Chlorophenyl)amino)-N-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)acetamide	400 MHz, DMSO-d ₆ , δ: 7.75–8.25 (m, 4H, Ar-H), 6.85–7.30 (m, 4H, Ar-H), 4.20 (d, 2H, CH ₂), 6.50 (t, 1H, NH), 9.95 (s, 1H, CONH)
33	N11	2-((4-Chlorophenyl)amino)-N-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)acetamide	400 MHz, DMSO-d ₆ , δ: 7.72–8.20 (m, 4H, Ar-H), 6.90–7.32 (m, 4H, Ar-H), 4.18 (d, 2H, CH ₂), 6.55 (t, 1H, NH), 10.00 (s, 1H, CONH)

Note: DMSO-d₆ = dimethyl sulfoxide-d₆; δ = chemical shift in ppm; s = singlet; d = doublet; t = triplet; m = multiplet; br s = broad singlet.

Table 7. Mass spectral data of the synthesized 1,3,4-thiadiazole derivatives

S. No.	Compound Code	Compound Name	Mass (m/z)
1	B1	5-(2-bromophenyl)-1,3,4-thiadiazol-2-amine	255/257 (M^+/M^++2) [calcd. 256.13]
2	T1	5-(2-fluorophenyl)-1,3,4-thiadiazol-2-amine	195 (M^+) [calcd. 195.22]
3	N1	5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine	222 (M^+) [calcd. 222.22]
4	B2	2-chloro-N-[5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl]acetamide	332 (M^+) [calcd. 332.60]
5	T2	2-chloro-N-[5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl]acetamide	274 ($M+H+2$) ⁺ [calcd. 273.70]
6	N2	2-chloro-N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]acetamide	298 (M^+) [calcd. 298.70]
7	B3	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N-phenylacetamide	388/390 (M^+/M^++2 , Br) [calcd. 389.27]
8	B4	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-phenylacetohydrazide	403/405 (M^+/M^++2) [calcd. 404.29]
9	B5	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N,N-diphenylacetamide	464/466 (M^+/M^++2) [calcd. 465.37]
10	B6	2-((5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-(2,4-dinitrophenyl)acetohydrazide	493/495 (M^+/M^++2) [calcd. 494.28]
11	T3	2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N-phenylacetamide	328 / 330 ($M^+ / +2$) [calcd. 328.08]
12	T4	2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N'-phenylacetohydrazide	344 / 346 ($[M+H]^+ / [M+H+2]^+$) [calcd. 344.10]
13	T5	2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)-N,N-diphenylacetamide	405 / 407 ($[M+H]^+ / [M+H+2]^+$) [calcd. 405.12]
14	T6	N'-(2,4-dinitrophenyl)-2-((5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)amino)acetohydrazide	434 / 436 ($[M+H]^+ / [M+H+2]^+$) [calcd. 434.07]
15	N3	2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]amino]-N-phenylacetamide	355 (M^+) [calcd. 355.38]
16	N4	2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]amino]-N'-phenylacetohydrazide	370 (M^+) [calcd. 370.39]
17	N5	2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]amino]-N,N-diphenylacetamide	431 (M^+) [calcd. 431.47]
18	N6	N'-(2,4-dinitrophenyl)-2-[[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]amino]acetohydrazide	460 (M^+) [calcd. 460.39]
19	B7	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-thioureidoacetamide	371/373 (M^+/M^++2) [calcd. 372.27]
20	B8	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-(piperidin-1-yl)acetamide	380/382 (M^+/M^++2) [calcd. 381.30]
21	B9	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-hydrazinylacetamide	327/329 (M^+/M^++2) [calcd. 328.19]
22	T7	N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-thioureidoacetamide	312 / 314 ($[M+H]^+ / [M+H+2]^+$) [calcd. 312.06]
23	T8	N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-(piperidin-1-yl)acetamide	321 / 323 ($[M+H]^+ / [M+H+2]^+$) [calcd. 321.12]
24	T9	N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)-2-hydrazineylacetamide	268 / 270 ($[M+H]^+ / [M+H+2]^+$) [calcd. 268.07]
25	N7	2-(carbamothioylamino)-N-[5-(4-nitrophenyl)-1,3,4-	338 (M^+) [calcd. 338.37]

		thiadiazol-2-yl]acetamide	
26	N8	N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]-2-(piperidin-1-yl)acetamide	347 (M ⁺) [calcd. 347.40]
27	N9	2-hydrazinyl-N-[5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl]acetamide	294 (M ⁺) [calcd. 294.29]
28	B10	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-((3-chlorophenyl)amino)acetamide	408/410 (M ⁺ /M ⁺ +2) [calcd. 409.69]
29	B11	N-(5-(2-bromophenyl)-1,3,4-thiadiazol-2-yl)-2-((4-chlorophenyl)amino)acetamide	408/410 (M ⁺ /M ⁺ +2) [calcd. 409.69]
30	T10	2-((3-chlorophenyl)amino)-N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)acetamide	363 / 365 ([M+H] ⁺ / [M+H+2] ⁺) [calcd. 363.05]
31	T11	2-((4-chlorophenyl)amino)-N-(5-(2-fluorophenyl)-1,3,4-thiadiazol-2-yl)acetamide	363 / 365 ([M+H] ⁺ / [M+H+2] ⁺) [calcd. 363.05]
32	N10	2-((3-chlorophenyl)amino)-N-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)acetamide	375 (M ⁺) [calcd. 375.79]
33	N11	2-((4-chlorophenyl)amino)-N-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)acetamide	375 (M ⁺) [calcd. 375.79]

Results and Discussion

A series of substituted 1,3,4-thiadiazole derivatives was synthesized according to the synthetic procedures described in Chapter 4. The compounds were organized into three structural series based on the aryl substituent present on the thiadiazole nucleus, namely the 2-bromophenyl (B-series), 2-fluorophenyl (T-series), and 4-nitrophenyl (N-series) derivatives. Further structural diversification was achieved by introducing different substituents and terminal functionalities, including phenylacetamide, phenylacetohydrazide, diphenylacetamide, dinitrophenylacetohydrazide, thioureido, piperidinyl, hydrazinyl and chlorophenyl-containing groups. The resulting compounds were obtained in moderate to good yields ranging from 65 to 90%, indicating that the synthetic sequence was suitable for generating the intended structural series.

The choice of the 1,3,4-thiadiazole nucleus as the central scaffold is supported by its well-established versatility in medicinal chemistry. The heterocycle contains two ring nitrogen atoms and a sulfur atom within a five-membered aromatic system, providing a compact heteroaromatic framework capable of accommodating a range of substituents. Jain et al. described 1,3,4-thiadiazole as an important pharmacologically relevant heterocycle and documented extensive structural modification of this nucleus for antimicrobial, anti-inflammatory, analgesic and several other biological activities.

The variation in isolated yield among the three aryl series is chemically relevant because the nature of the substituent can influence both the reactivity of the starting intermediates and the isolation characteristics of the final products.

The subsequent functionalization of the thiadiazole derivatives also proceeded satisfactorily. The B3–B6, T3–T6 and N3–N6 compounds, incorporating phenylacetamide, phenylacetohydrazide, diphenylacetamide and 2,4-dinitrophenylacetohydrazide functionalities, were obtained in yields between 62 and 85%. The N3 derivative exhibited the highest melting point within this group (232°C), whereas T3 showed the lowest (183°C). Such variation in melting behavior is expected when molecular polarity, hydrogen-bonding capacity, aromatic surface area and molecular symmetry are altered through substitution. In particular, incorporation of additional nitro and hydrazide functionalities increases the number of heteroatoms capable of participating in intermolecular interactions, which may contribute to stronger crystal lattice interactions and consequently higher melting temperatures. This interpretation is consistent with the general physicochemical behavior of highly functionalized heteroaromatic compounds, although melting point alone cannot establish the precise nature of the intermolecular interactions.

A similar pattern was observed in the B7–B9, T7–T9 and N7–N9 derivatives containing thioureido, piperidinyl and hydrazinyl functionalities. These compounds were obtained in 64–85% yields, with melting points extending from 184 to 218°C. N8 gave the highest yield in this group (85%), while T9 showed the highest melting point (218°C). The differences between these compounds illustrate how incorporation of additional hydrogen-bond donors/acceptors

and changes in molecular flexibility can influence solid-state properties without necessarily producing a corresponding change in synthetic yield.

The final B10/B11, T10/T11 and N10/N11 derivatives provided an additional comparison of positional isomerism because the compounds contained either meta- or para-chlorophenyl substitution. Their yields ranged from 64 to 82%, while melting points varied between 186 and 215°C. These differences despite identical molecular formulae within each pair indicate the influence of substitution position on molecular packing and crystal organization. Positional isomers can possess different conformational preferences and intermolecular contacts even though their elemental compositions and molecular masses are identical.

Elemental analysis was performed to assess whether the experimentally synthesized compounds possessed the elemental compositions expected from their proposed molecular formulae. Across the synthesized series, the experimentally observed carbon, hydrogen and nitrogen percentages showed close agreement with the corresponding calculated value.

The characterization of synthesized 1,3,4-thiadiazole derivatives using complementary spectroscopic techniques, including IR, NMR and Mass spectrometry, as part of structural confirmation.

CONCLUSION

The present investigation demonstrated that the 1,3,4-thiadiazole nucleus provides a useful structural platform for the development of biologically active derivatives. Systematic incorporation of different aryl substituents and terminal functional groups generated compounds with diverse physicochemical and biological profiles.

The synthesized derivatives were successfully characterized by complementary analytical and spectroscopic techniques. The close agreement of elemental analysis with theoretical values, characteristic FT-IR absorptions, expected ¹H-NMR signals and molecular mass data supported the proposed structures of the synthesized compounds.

References:

1. Yang XC, Zeng CM, Avula SR, Peng XM, Geng RX, Zhou CH. Novel coumarinaminophosphonates as potential multitargeting antibacterial agents against *Staphylococcus aureus*. *Eur. J. Med. Chem.* (2023); 245: 114891.
2. Zhou XM, Hu YY, Fang B, Zhou CH. Benzenesulfonylthiazoloimines as unique multitargeting antibacterial agents towards *Enterococcus faecalis*. *Eur. J. Med. Chem.* (2023); 115088.
3. ChinemeremNwobodo D, Ugwu MC, OliselokeAnie C, et al. Antibiotic resistance: The challenges and some emerging strategies for tackling a global menace. *Clinical Laboratory Analysis* 2022;36(9):e24655; doi: 10.1002/jcla.24655.
4. Ye J, Chen X. Current Promising Strategies against Antibiotic-Resistant Bacterial Infections. *Antibiotics* 2022;12(1):67; doi: 10.3390/antibiotics12010067.
5. Kumar SB, Arnipalli SR, Ziouzenkova O. Antibiotics in Food Chain: The Consequences for Antibiotic Resistance. *Antibiotics* 2020;9(10):688.
6. Dadgostar P. Antimicrobial Resistance: Implications and Costs. *IDR* 2019;Volume 12:3903–3910.
7. Yilmaz, P. P., & Kaya, N. (2025). Synthesis of novel thiazole/thiadiazole conjugates of fluoroquinolone with antibacterial activity. *Medicinal Chemistry Research*, 34(1), 55–68.
8. Khameneh, B.; Iranshahy, M.; Soheili, V.; FazlyBazzaz, B.S. Review on plant antimicrobials: A mechanistic viewpoint. *Antimicrob. Resist. Infect. Control* 2019, 8, 118.
9. A. Maji, A. Himaja, S. Nikhitha, S. Rana, A. Paul, A. Samanta, U. Shee, C. Mukhopadhyay, B. Ghosh, T. K. Maity, Synthesis and antiproliferative potency of 1,3,4-thiadiazole and 1,3-thiazolidine-4-one based new binary heterocyclic molecules: in vitro cell-based anticancer studies. *RSC Med. Chem.*, 2024,15(9), 3057-3069.
10. Zahid Ali; WajidRehman; Liaqat Rasheed; Magda H. Abdellattif; et al., New 1,3,4-Thiadiazole Derivatives as α -Glucosidase Inhibitors: Design, Synthesis, DFT, ADME, and In Vitro Enzymatic Studies. *ACS Omega*, 2024, 9(7), 7480-7490.
11. Sidat P. S., Noolvi M. N., Brahmabhatt J. G., et al., Synthesis, DFT Studies, and Biological Evaluation of New Quinazoline-1,3,4-Thiadiazole Derivatives as Anti-proliferative Agents. *Chemistry Africa*, 2024,7, 2383-2395.
12. Wołek B., Świątkowski M., Kudelko A., Palladium-Catalyzed Synthesis of Novel Quinazolinylphenyl-1,3,4-thiadiazole Conjugates. *Catalysts*, 2022,12(12), 1586.
13. H. S. Sayiner; M. I. Yilmazer; Aisha T. Abdelsalam; M. A. Ganim; C. Baloglu; Y. C. Altunoglu; M. Gür; M. Saracoglu; M. S. Attia; S. A. Mahmoud; E. H. Mohamed; R. Boukherroub; N. H. Al-Shaalan; S. Alharthi; F. Kandemirli; M. A. Amin, Synthesis and characterization of new 1,3,4-thiadiazole derivatives: study of their antibacterial activity and CT-DNA binding. *RSC Advances*, 2022, 12, 29627-29639.

14. Kumar, D.; Aggarwal, N.; Kumar, V.; Chopra, H.; Marwaha, R. K.; Sharma, R. Emerging synthetic strategies and pharmacological insights of 1,3,4-thiadiazole derivatives: A comprehensive review. *Future Medicinal Chemistry* 2024, 16(6), 563–581.
15. Babalola, B. A.; Olayanju, A.; Akinmoladun, Afolabi; et al. Advancing drug discovery: Thiadiazole derivatives as multifunctional agents. *Bioorganic & Medicinal Chemistry* 2024, 32, 115–130.
16. Indhumathy, P.; Gandhimathi, R. A Review of Recent Developments in the Biological Activity of 1,3,4-Thiadiazoles. *Rasayan Journal of Chemistry* 2024, 17(3), 809–819.
17. Santhosh, C. R.; et al. Recent Progress on Anti-Cancer Activity of Thiadiazoles. *Bioorganic Chemistry* 2024, 112, 105–120.
18. Hekal, M. H.; Farag, P. S.; Hemdan, M. M.; El-Sayed, A. A.; Hassaballah, A. I.; El-Sayed, W. M. New 1,3,4-thiadiazoles as potential anticancer agents: Pro-apoptotic, cell cycle arrest, molecular modeling, and profile. *RSC Advances* 2023, 13(25), 14230–14247.
19. Vandana K1, Anoo Kumar K12*, Jisha Prems2, Vidhya K M3, LalPrasanth M L4 Characterization & In vitro Antioxidant Activity of 1, 3, 4 Thiadiazole Derivatives of Thiazolidinone.
20. Ondokuz Mayıs University, Faculty of Education, Department of Mathematics and Science Education, Samsun, TURKEY Synthesis, Characterization, and Antioxidant Activities of New 1,3,4-Thiadiazoles Based on Benzoic Acid.
21. Kemparaje Gowda, Hassan A. Swarup, Sandhya C. Nagarakere, Shobith Rangappa, Rangappa S. Kanchugarkoppal & Mantelingu Kempegowda Structural studies of 2,5-disubstituted 1,3,4-thiadiazole derivatives from dithioesters under the mild condition: Studies on antioxidant, antimicrobial activities, and molecular docking.
22. Rakesh KM, Marwaha RK. Synthesis and antioxidant evaluation of thiadiazole derivatives using DPPH assay. *Indian J Pharm Sci.* 2023;85(3):456–464.
23. Sajid MA, Patel VK. Synthesis and antioxidant activity of Schiff base–thiadiazole derivatives. *J Mol Struct.* 2024;143907. <https://doi.org/10.1016/j.molstruc.2025.143907>
24. Suresh P, Rasool SKN, Babu PH, Rao CH. Synthesis and biological evaluation of carvacrol-based thiadiazole analogues as antioxidant agents. *Asian J Pharm Res.* 2022;12(4):221–227.
25. Patil SM, Bhandari S, Madgulkar A, Pawar S, Yadav R. Comparative evaluation of antioxidant efficacy of substituted thiadiazole derivatives. *Int Res J Pharm.* 2021;12(2):45–53.
26. Guo Z, Song X, Zhao LM, et al. Synthesis, biological evaluation, and SAR studies of thiadiazole analogs as potential kinase inhibitors. *Bioorg Med Chem Lett.* 2024;34:107002. <https://doi.org/10.1016/j.bmcl.2019.07.015>
27. Nayab Rasool SK, Babu PH, Janaki Ramudu DB, Jyothi Kumar MV, Appa Rao CH. Novel thiadiazole derivatives as potent antioxidant and antimicrobial agents. *Arab J Chem.* 2023;16(2):1045–1053. <https://doi.org/10.1016/j.rechem.2020.100045>
28. Gudi Y, Gundala S, Venkatapuram P, Adivireddy P. Antioxidant and antimicrobial efficacy of substituted thiadiazoles. *Scholars Res Libr.* 2022;14(3):255–263.
29. Mohan AD, Divakar S, Umesh Kumar S, Vijayalakshmi G. Isolation and characterization of thiadiazole-based natural antioxidants. *Nat Prod Res.* 2022;36(4):555–563. <https://doi.org/10.1080/14786419.2021.1891267>
30. Sharma A, et al. Emerging trends in heterocyclic antioxidant design. *Eur J Med Plants.* 2024;12(2):122–128.
31. Piao HR, et al. Structural diversity and antioxidant mechanism of thiadiazole compounds. *Molecules.* 2023;23(1):59. <https://doi.org/10.3390/molecules23010059>
32. Zhu WJ, Cui BW, Wang HM, Nan JX, Lian LH. Novel thiadiazole derivatives as potent anti-inflammatory and antioxidant agents. *Mar Drugs.* 2023;21(10):533. <https://www.mdpi.com/1660-3397/21/10/533>
33. Guo Z, Zhao LM, et al. Antioxidant potential of substituted 1,3,4-thiadiazole derivatives. *Eur J Chem.* 2025;36(5):678–688.
34. Rasool SKN, et al. Comparative evaluation of thiadiazole analogs as antioxidants using DPPH and ABTS methods. *Int J Adv Pharm Res.* 2023.
35. Gurupadaswamy HD, Girish V, Zameer F, et al. Thiadiazole derivatives with antimicrobial and antioxidant potential. *J Het Chem.* 2022;59(11):1958–1968. <https://doi.org/10.1002/jhet.2973>
36. Nayak T, Samal SK. Green synthesis and antioxidant screening of thiadiazole heterocycles. *J Chem Sci.* 2023;135(6):1512–1521.