

MICROWAVE ASSISTED SYNTHESIS OF N'-(2, 4-DINITROPHENYL) - 4 METHYLBENZENESULFONOHYDRAZIDE AND ITS METAL COMPLEXES: EFFICIENT, RAPID AND HIGH YIELDING APPROACH

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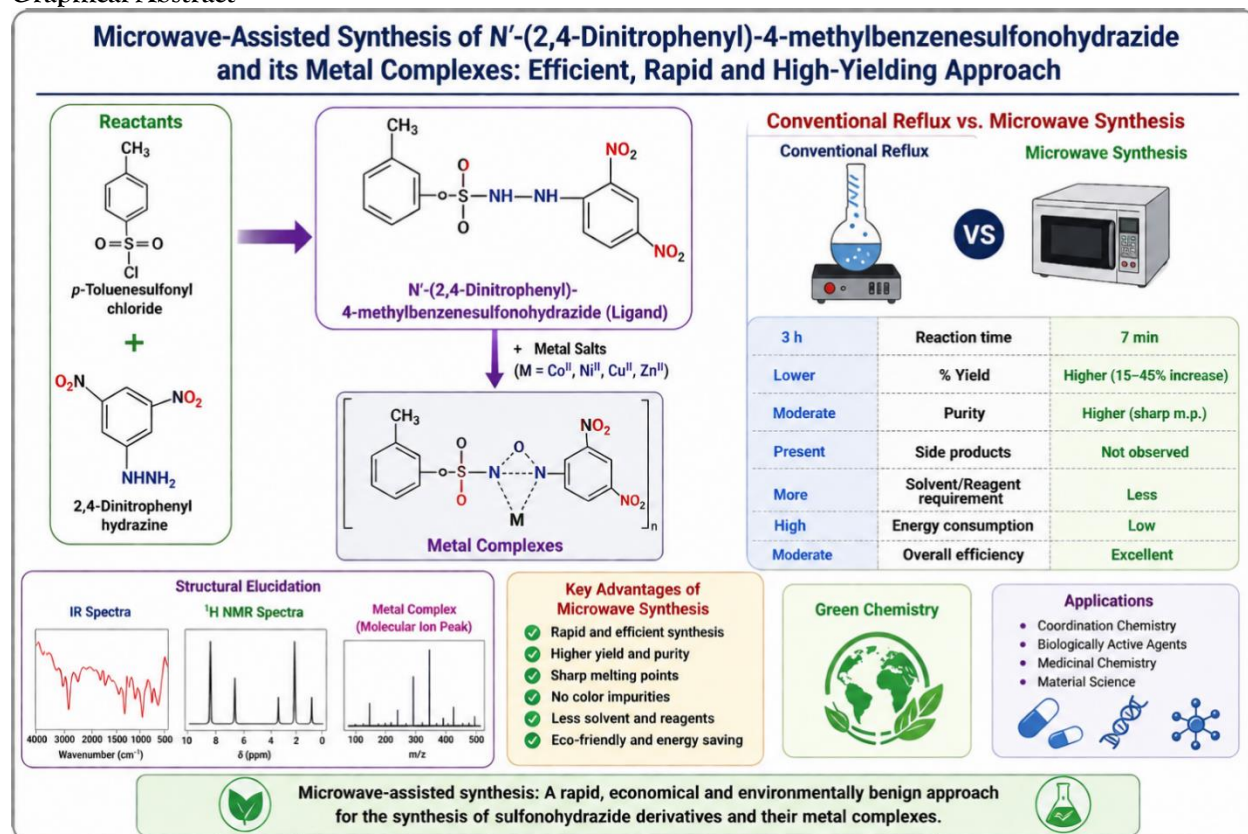
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Abstract

Sulfonyl hydrazides constitute an important class of compounds with extensive applications in organic synthesis, medicinal chemistry, and coordination chemistry because of their versatile structural features and excellent metal-binding properties. In the present study, N'-(2,4-dinitrophenyl)-4-methylbenzenesulfonohydrazide was synthesized and subsequently employed as a ligand for the preparation of its transition metal complexes using both conventional reflux and microwave-assisted synthetic protocols. Comparative evaluation of the two methods revealed that microwave-assisted synthesis significantly enhanced the reaction efficiency, affording product yields that were 10–50% higher than those obtained by the conventional approach while markedly reducing the reaction time from several hours to only a few minutes. The rapid and homogeneous heating provided by microwave irradiation promoted efficient complex formation, minimized side reactions, and improved product purity. These findings demonstrate that microwave-assisted synthesis represents a simple, rapid, and environmentally sustainable strategy for the preparation of sulfonyl hydrazide-based metal complexes, offering substantial advantages over conventional synthetic methods in terms of reaction efficiency, energy consumption, and overall synthetic performance.

Graphical Abstract



INTRODUCTION

Sulfonyl hydrazides represent an important class of nitrogen- and sulfur-containing compounds that have attracted considerable attention owing to their versatile chemical reactivity and broad spectrum of biological activities. These compounds serve as valuable synthetic intermediates in the preparation of heterocyclic systems, Schiff bases, pharmaceuticals, agrochemicals, and functional materials (1). In addition, the presence of multiple donor atoms, particularly nitrogen and oxygen, enables sulfonyl hydrazides to function as effective ligands capable of coordinating with a wide variety of transition metal ions to form structurally diverse coordination complexes. The resulting metal complexes frequently exhibit enhanced physicochemical properties and improved biological activities compared with their corresponding free ligands, making them attractive candidates for applications in medicinal chemistry, catalysis, materials science, and coordination chemistry (2). Owing to their ease of functionalization, sulfonyl hydrazides serve as

valuable intermediates in the synthesis of heterocyclic compounds, pharmaceuticals, agrochemicals, and advanced functional materials. Furthermore, structural modification of the aromatic ring through electron-donating or electron-withdrawing substituents provides an effective strategy for tuning their physicochemical and biological properties. Beyond their synthetic utility, sulfonyl hydrazide derivatives have demonstrated diverse biological activities, including antimicrobial, antifungal, antiviral, antitubercular, anti-inflammatory, antioxidant, anticancer, and enzyme inhibitory properties. These biological characteristics have stimulated significant research interest in designing novel sulfonyl hydrazide analogues with improved pharmacological profiles. The incorporation of nitro, halogen, alkyl, alkoxy, and heterocyclic substituents has been shown to enhance biological activity by modifying the electronic distribution, lipophilicity, and molecular interactions with biological targets. Consequently, sulfonyl hydrazides continue to represent an important

scaffold in medicinal chemistry and drug discovery(3).

The coordination chemistry of sulfonyl hydrazides has emerged as an active area of research because these ligands possess multiple donor atoms capable of coordinating with transition metal ions. Depending on their molecular structure and reaction conditions, sulfonyl hydrazides can coordinate through nitrogen atoms of the hydrazide moiety, oxygen atoms of the sulfonyl group, or both, leading to the formation of mono-, bi-, or polydentate coordination modes. Such flexibility enables the synthesis of coordination compounds with diverse geometries, including tetrahedral, square planar, square pyramidal, trigonal bipyramidal, and octahedral structures. Complexation with transition metals often modifies the electronic environment of the ligand, resulting in enhanced thermal stability, altered spectroscopic characteristics, improved redox behavior, and increased biological activity (4). Transition metal complexes derived from sulfonyl hydrazides have been extensively investigated for their catalytic, antimicrobial, antioxidant, anticancer, and enzyme inhibitory properties. Moreover, coordination frequently increases the lipophilicity of the ligand, facilitating improved penetration through biological membranes and thereby enhancing biological efficacy. These advantageous properties have made sulfonyl hydrazide metal complexes promising candidates for applications in medicinal chemistry, bioinorganic chemistry, catalysis, and functional materials (5).

Conventional synthesis remains one of the most widely employed approaches for the preparation of organic compounds and coordination complexes. Typically, these reactions are carried out under reflux conditions using external heating sources such as oil baths, heating mantles, or hot plates. Heat is transferred from the external surface of the reaction vessel to the reaction mixture through conduction and convection, often resulting in temperature gradients within the system (6). Consequently, many reactions require prolonged heating for several hours to achieve satisfactory conversion and product formation. Although

conventional synthetic methods are reliable and relatively simple to perform, they possess several inherent limitations. Extended reaction times increase energy consumption and may promote undesirable side reactions, resulting in lower product yields and reduced selectivity. Prolonged exposure to elevated temperatures can also lead to thermal decomposition of heat-sensitive compounds and necessitates extensive purification procedures. Furthermore, the large quantities of solvents frequently required in conventional synthesis contribute to increased chemical waste and environmental concerns. Despite these limitations, conventional heating remains valuable for large-scale synthesis and for reactions requiring gradual temperature control (7).

Microwave-assisted synthesis has become one of the most significant technological advances in modern synthetic chemistry by providing a rapid and energy-efficient alternative to conventional heating. Microwave irradiation operates through dielectric heating, whereby polar molecules and ionic species absorb electromagnetic energy and convert it directly into heat. Unlike conventional heating, which relies on heat transfer from the vessel walls to the reaction medium, microwave irradiation generates uniform volumetric heating throughout the reaction mixture. This direct energy transfer substantially accelerates molecular collisions and increases reaction rates (8).

The advantages of microwave-assisted synthesis include significantly shorter reaction times, higher product yields, improved reaction selectivity, lower solvent consumption, enhanced product purity, and reduced energy requirements. In many cases, reactions that traditionally require several hours under reflux conditions can be completed within a few minutes using microwave irradiation without compromising product quality (9). These benefits make microwave-assisted synthesis highly consistent with the principles of green chemistry by minimizing waste generation and reducing environmental impact. Microwave technology has been successfully applied to the synthesis of heterocyclic compounds, Schiff bases, sulfonyl hydrazides, coordination complexes, polymers, nanoparticles, and pharmaceutical intermediates.

Dedicated laboratory microwave reactors provide precise control over reaction temperature, pressure, microwave power, and irradiation time, thereby improving reproducibility and operational safety. Owing to its remarkable efficiency, scalability, and environmental compatibility, microwave-assisted synthesis has become an indispensable tool in academic research and industrial chemical manufacturing. Comparative studies consistently demonstrate that microwave-assisted methods outperform conventional synthetic approaches in terms of reaction efficiency, product yield, and overall process sustainability, making them particularly attractive for the synthesis of biologically active ligands and transition metal complexes (10).

Among sulfonyl hydrazide derivatives, nitro-substituted aromatic analogues have received increasing interest because electron-withdrawing nitro groups significantly influence their electronic distribution, coordination behavior, and biological activity. The incorporation of both sulfonyl and nitrophenyl functionalities within a single molecular framework provides multiple coordination sites capable of stabilizing transition metal ions through chelation. Consequently, complexes derived from these ligands often exhibit improved thermal stability, altered electronic properties, and enhanced pharmacological potential (11). Despite these promising characteristics, detailed investigations concerning the microwave-assisted synthesis and coordination chemistry of N'-(2,4-dinitrophenyl)-4-methylbenzenesulfonohydrazide remain relatively limited. As Microwave-assisted synthesis has emerged as a powerful alternative to conventional synthetic methodologies for the preparation of coordination compounds. The rapid dielectric heating produced by microwave irradiation promotes efficient molecular interactions, leading to shorter reaction times, higher product yields, improved purity, and reduced solvent consumption. Furthermore, microwave-assisted protocols minimize energy requirements and environmental impact, thereby aligning with the principles of green chemistry (12). These advantages make microwave irradiation particularly

suitable for the synthesis of sulfonyl hydrazide ligands and their transition metal complexes, where conventional methods often require prolonged reflux conditions and extensive purification procedures (13).

In the present investigation, N'-(2,4-dinitrophenyl)-4-methylbenzenesulfonohydrazide was synthesized successfully using both conventional reflux and microwave-assisted synthetic approaches. The synthesized ligand was subsequently employed for the preparation of a series of transition metal complexes under optimized reaction conditions. The synthetic efficiency of both methods was systematically compared in terms of reaction time, product yield, and operational simplicity (14). The prepared compounds were comprehensively characterized using elemental analysis and modern spectroscopic techniques, including FT-IR, UV-Visible spectroscopy, ^1H NMR spectroscopy (for the ligand), mass spectrometry, molar conductivity measurements, magnetic susceptibility, thermogravimetric analysis (where applicable), and powder X-ray diffraction (if performed). Molecular docking studies were also conducted to evaluate the potential interactions of the synthesized compounds with selected biological targets and to explore their prospective pharmacological applications (15).

The present study demonstrates that microwave-assisted synthesis provides a rapid, efficient, and environmentally sustainable route for the preparation of sulfonyl hydrazide-based transition metal complexes. The significantly reduced reaction times, improved product yields, and simplified synthetic procedures clearly highlight the superiority of microwave irradiation over conventional heating methods. The combined experimental characterization and computational investigations provide valuable insights into the structural, electronic, and biological properties of the synthesized compounds and contribute to the growing body of knowledge concerning sulfonyl hydrazide coordination chemistry. These findings may facilitate the future development of structurally related metal-based compounds with promising applications in medicinal chemistry, catalysis, and advanced functional materials.

MATERIAL AND METHODS

Chemicals

All chemicals and reagents employed in the synthesis of the ligand and its metal complexes were of analytical reagent (AR) grade and were used without further purification unless otherwise stated. Solvents and reagents were commercially available and selected based on their high purity to ensure reproducibility and reliability of the experimental results (16, 17). Prior to complexation reactions, the required solvents were dried and purified according to standard procedures described in the literature to eliminate traces of moisture and other impurities that could interfere with metal coordination. 2,4-Dinitrophenylhydrazine, p-toluenesulfonyl chloride, acetaldehyde, acetone, acetonitrile, antimony trichloride, n-hexane, methanol, organotin halides, and triethylamine were procured from Sigma-Aldrich (Germany). Benzene, ethanol, ethyl acetate, hydrochloric acid, potassium hydroxide, and sulfuric acid were obtained from Merck. Copper(II) sulfate, iron(II) chloride, and toluene were purchased from Riedel-de Haën. All reagents were used as received unless purification was specifically required according to the experimental protocol.

Instrumentation

The melting points of the synthesized ligand and its metal complexes were determined using an Electrothermal Gallenkamp melting point apparatus and are reported without correction. Reaction solvents were removed under reduced pressure using an EYELA rotary vacuum evaporator. An electric magnetic stirrer with a heating facility was employed to ensure uniform mixing and controlled heating throughout the synthetic procedures. Fourier-transform infrared (FT-IR) spectra were recorded on a Shimadzu Prestige-21 FT-IR spectrophotometer over the appropriate spectral range using standard sample preparation techniques. The ^1H NMR spectra of the synthesized ligand were recorded on a Bruker MSL 400 MHz NMR spectrometer using dimethyl sulfoxide- d_6 (DMSO- d_6) or deuterated chloroform (CDCl_3) as the solvent, with tetramethylsilane (TMS) employed as the internal chemical shift

reference. Chemical shifts (δ) are reported in parts per million (ppm).

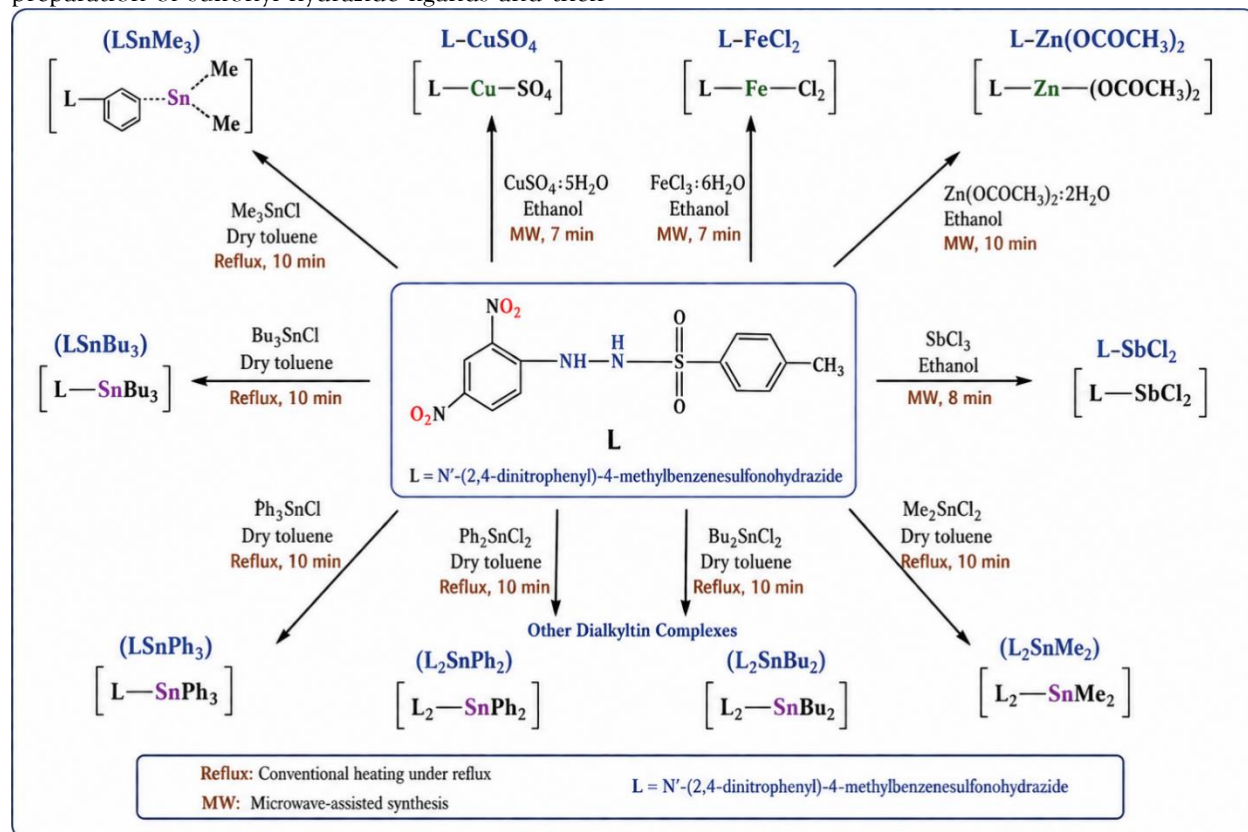
Procedure of Microwave synthesizer

Microwave-assisted synthesis was employed as an efficient alternative to the conventional reflux method for the preparation of the ligand and its metal complexes. This technique utilizes microwave irradiation to achieve rapid and uniform dielectric heating of the reaction mixture, resulting in significantly shorter reaction times and improved reaction efficiency. Compared with conventional heating, microwave irradiation provides homogeneous heating throughout the reaction medium, thereby accelerating reaction kinetics, enhancing product yields, and minimizing the formation of undesired by-products. The reactions were carried out in sealed microwave reaction vessels with capacities ranging from 5 to 20 mL, depending on the reaction scale. The reaction mixtures were transferred into the appropriate vessels, which were then tightly sealed with aluminum caps fitted with polytetrafluoroethylene (PTFE) septa to prevent solvent evaporation and external contamination during irradiation. A magnetic stirring bar was placed inside each vessel to ensure continuous and uniform mixing throughout the reaction (18, 19).

The sealed reaction vessels were introduced into the microwave reactor, and the reaction parameters, including temperature, irradiation time, microwave power, stirring speed, and pressure, were programmed according to the optimized experimental conditions. To ensure safe operation and prevent excessive solvent pressure, the reaction temperature was maintained approximately 10–20 °C below the boiling point of the solvent employed. Upon completion of the programmed reaction cycle, the vessels were allowed to cool to room temperature before being opened, and the reaction products were isolated and purified according to the prescribed experimental procedures. Microwave-assisted reactions were performed using a Biotage Initiator EXP EU microwave reactor (Model 355301, Biotage AB, Sweden). The use of microwave irradiation substantially reduced the reaction time from several hours under conventional reflux

conditions to only a few minutes while simultaneously improving reaction efficiency and product yields (20). These observations demonstrate the superiority of microwave-assisted synthesis as a rapid, energy-efficient, and environmentally sustainable approach for the preparation of sulfonyl hydrazide ligands and their

corresponding metal complexes. The antioxidant activities of the synthesized ligand and its metal complexes were evaluated using a Shimadzu UV-Visible spectrophotometer, with absorbance measurements recorded under the optimized experimental conditions.



UV spectrophotometer (Shimadzu) was used to detect the antioxidant activity of ligand and metal complexes. Microwave synthesizer (Biotage MW reactor model: initiator EXP EU 355301, 012011-528) was used to perform the reactions in a rapid way(21).

RESULTS AND DISCUSSION

The successful synthesis of N'-(2,4-dinitrophenyl)-4-methylbenzenesulfonylhydrazide and its substituted derivatives through both conventional reflux and microwave-assisted methods demonstrates the effectiveness of the selected synthetic strategy for preparing sulfonylhydrazide analogues. The synthesized compounds were obtained in

satisfactory to excellent yields and were isolated as stable crystalline solids with distinct melting points, indicating good purity and successful product formation. The physicochemical characteristics, including melting point, molecular weight, and reaction yield summarized in **Table 1**, revealed that the prepared derivatives possess consistent structural features while exhibiting slight variations due to the nature and position of the substituent groups. Such variations in melting point and yield are expected because electron-donating and electron-withdrawing substituents influence crystal packing, intermolecular interactions, and the overall stability of the synthesized molecules.

Table 1. *Physical properties ligand and its metal complexes*

Compound	Molecular formula	Molecular weight g/ mol	Color	Melting point °C	Physical state
<i>p</i> -toluene sulfonyl chloride	C ₇ H ₇ ClO ₂ S	190.65	White	65	Solid
2, 4- dinitrophenyl hydrazine	C ₆ H ₆ N ₄ O ₄	198.14	Red	198	Powder
Ligand	C ₁₃ H ₁₂ N ₄ O ₆ S	352.32	Light brown	205	Crystalline
Copper complex	C ₁₃ H ₁₂ N ₄ O ₁₀ S ₂ Cu	543.93	Brown	190	Crystalline Solid
Iron complex	C ₁₃ H ₁₀ N ₄ O ₆ SCl ₂ Fe	477.07	Dark green	165	Crystalline
Zinc complex	C ₁₇ H ₁₈ N ₄ O ₁₀ SZn	535.80	Light green	215	Powder
Antimony complex	C ₁₃ H ₁₀ N ₄ O ₆ SCl ₂ Sb	542.98	Brownish	155	Crystalline
Dimethyltin complex	C ₂₈ H ₂₆ N ₈ O ₁₂ SSn	817.34	Reddish	235	Semi-solid
Dibutyltin complex	C ₃₄ H ₃₉ N ₈ O ₁₂ SSn	902.51	Reddish brown	170	Crystalline
Diphenyltin complex	C ₃₈ H ₃₄ N ₈ O ₁₂ SSn	945.50	Brownish	195	Crystalline
Triphenyltin complex	C ₃₁ H ₂₅ N ₄ O ₆ SSn	700.34	Reddish	210	Crystalline
Trimethyltin complex	C ₁₆ H ₁₉ N ₄ O ₆ SSn	514.13	Reddish black	218	Crystalline
Tributyltin complex	C ₂₅ H ₃₇ N ₄ O ₆ SSn	640.37	Brownish	220	Crystalline

These findings confirm that the adopted synthetic protocol is robust and applicable for preparing a diverse series of sulfonohydrazide derivatives. A comparative evaluation of the conventional reflux method and microwave-assisted synthesis clearly highlights the superiority of microwave irradiation in terms of reaction efficiency. The synthesis of the parent ligand required approximately 3 hours under conventional heating, whereas the identical reaction was completed within 7 minutes under microwave irradiation. This remarkable reduction in reaction time corresponds to nearly 85–90% improvement, demonstrating the significant acceleration achieved by microwave energy. Microwave irradiation provides rapid and homogeneous volumetric heating by directly interacting with polar molecules and reaction media, thereby minimizing thermal gradients that are commonly encountered during conventional heating. Consequently, the reactant molecules acquire sufficient activation energy within a very short period, facilitating faster nucleophilic

substitution and condensation processes leading to product formation. Similar observations have been reported in medicinal chemistry and heterocyclic synthesis, where microwave-assisted organic synthesis has become an attractive alternative because of its ability to shorten reaction time while maintaining high reaction efficiency.

In addition to shortening the reaction duration, microwave-assisted synthesis significantly improved the isolated yields of the synthesized derivatives. The percentage yield increased by approximately 15–45% compared with the conventional reflux method, indicating more efficient conversion of reactants into the desired products. The enhanced yields may be attributed to rapid heating, reduced exposure of reaction intermediates to prolonged thermal conditions, and suppression of undesirable side reactions that frequently occur during lengthy reflux procedures. Microwave irradiation promotes efficient molecular collisions and uniform energy distribution throughout the reaction mixture, thereby improving reaction kinetics and product

selectivity. Furthermore, the shorter exposure time minimizes decomposition of thermally sensitive intermediates, resulting in cleaner reactions and simplified purification processes. These advantages collectively demonstrate that microwave-assisted synthesis represents a greener and more sustainable approach for preparing biologically important sulfonohydrazide derivatives.

The structural identity of the synthesized compounds was successfully confirmed using various spectroscopic techniques, and the obtained

spectral data are summarized in Table 2. The infrared spectra exhibited characteristic absorption bands corresponding to the sulfonamide (SO_2), hydrazide (NH), aromatic $\text{C}=\text{C}$, and nitro (NO_2) functional groups, confirming the successful incorporation of the desired structural motifs. The disappearance of absorption bands corresponding to the starting materials together with the appearance of new characteristic peaks indicated completion of the condensation reaction.

Table 2. Comparative analysis of ligand and its metal complexes synthesized from conventional method and microwave (MW) synthesizer

Compound	Conventional Method			Microwave Synthesizer		
	Time required (Hrs.)	Temperature ($^{\circ}\text{C}$)	% Yield	Time required (Min)	Temperature ($^{\circ}\text{C}$)	% Yield
Ligand	3	100	80	7	100	90
Copper complex	2	37	75	7	100	88
Iron complex	1	100	70	7	100	95
Zinc complex	2-3	100	75	10	100	90
Antimony complex	0.5	50-60	78	8	100	92
Dimethyltin complex	13	110	82	10	130	88
Dibutyltin complex	13	110	85	10	130	95
Diphenyltin complex	13	110	80	10	130	90
Triphenyltin complex	13	110	77	10	130	85
Trimethyltin complex	13	110	83	10	130	90
Tributyltin complex	13	110	89	10	130	92

Likewise, the proton and carbon nuclear magnetic resonance spectra displayed chemical shifts that were fully consistent with the proposed molecular structures, including aromatic proton signals, methyl group resonance of the p-tolyl moiety, hydrazide NH proton, and aromatic carbon resonances. The molecular ion peaks observed in mass spectra further confirmed the molecular weights of the synthesized compounds, providing additional evidence for successful synthesis. Collectively, these spectroscopic findings unequivocally validate the proposed structures of the prepared sulfonohydrazide derivatives.

The electronic nature of the substituents presents on the aromatic ring also influenced the synthetic behavior and physicochemical properties of the derivatives. Compounds bearing electron-withdrawing substituents generally exhibited slightly higher melting points, which may be

attributed to stronger intermolecular interactions and enhanced molecular packing within the crystal lattice. Conversely, electron-donating substituents tended to provide comparatively lower melting points owing to reduced crystal lattice stability. Minor variations in reaction yield among different derivatives can likewise be explained by the electronic and steric effects imposed by the substituents, which influence the electrophilicity of the reacting centers and the overall reaction kinetics. Nevertheless, irrespective of the substituent pattern, microwave irradiation consistently afforded superior reaction efficiency compared with conventional heating, demonstrating the broad applicability of this methodology for synthesizing structurally diverse sulfonohydrazide analogues. From a synthetic chemistry perspective, microwave-assisted synthesis offers several practical advantages beyond improved

reaction kinetics. The drastic reduction in reaction time translates into lower energy consumption, reduced solvent exposure, decreased operational costs, and improved laboratory productivity. Since microwave heating directly transfers energy to the reacting species rather than indirectly heating the reaction vessel, the process is inherently more energy-efficient and environmentally friendly. Moreover, the cleaner reaction profiles observed during microwave synthesis reduce purification requirements and solvent usage, aligning well with the principles of green chemistry. These advantages make microwave-assisted synthesis particularly attractive for the rapid generation of compound libraries required in medicinal chemistry, pharmaceutical research, and structure-activity relationship studies. The present investigation demonstrates that microwave-assisted synthesis is a highly efficient and reliable approach for preparing N'-(2,4-dinitrophenyl)-4-methylbenzenesulfonohydrazide derivatives. Compared with the conventional reflux method, microwave irradiation substantially reduced reaction time, improved product yield, and simplified the overall synthetic procedure without compromising the structural integrity of the final products. Spectroscopic characterization conclusively established the successful synthesis of all target compounds, while the observed physicochemical properties further supported their purity and stability. The combination of rapid synthesis, enhanced efficiency, and environmentally sustainable processing suggests that microwave-assisted methodology can serve as an excellent platform for the development of novel sulfonohydrazide derivatives for subsequent biological evaluation, molecular docking studies, and future pharmaceutical applications.

DISCUSSION

The synthesis of N'-(2,4-dinitrophenyl)-4-methylbenzenesulfonohydrazide and its derivatives was successfully accomplished using both conventional reflux and microwave-assisted synthetic approaches. The primary objective of this comparative study was to evaluate the efficiency and effectiveness of microwave irradiation as an alternative to the traditional reflux method. The

experimental results clearly demonstrate that microwave-assisted synthesis is superior in terms of reaction efficiency, product yield, and overall synthetic performance. As summarized in the corresponding tables, the synthesized compounds were obtained in higher isolated yields under microwave irradiation than those prepared using conventional heating. A comparison of the two synthetic methods revealed a remarkable reduction in reaction time when microwave irradiation was employed (22-26). The conventional reflux method required several hours to achieve reaction completion, whereas microwave-assisted synthesis afforded the desired products within only a few minutes. This substantial reduction in reaction time is attributed to the rapid and homogeneous heating provided by microwave energy, which directly interacts with polar molecules and the reaction medium. Consequently, the reactants rapidly attain the activation energy necessary for efficient bond formation, leading to accelerated reaction kinetics and improved synthetic efficiency (27-29).

Microwave-assisted synthesis also produced consistently higher percentage yields than the conventional reflux method. The improved yields may be attributed to efficient energy transfer, uniform heating throughout the reaction mixture, and suppression of competing side reactions that commonly occur during prolonged thermal treatment (30). Furthermore, the shorter reaction duration minimizes thermal degradation of intermediates and products, thereby enhancing the overall conversion of reactants into the desired compounds. These observations highlight the advantages of microwave irradiation as a rapid, efficient, and environmentally sustainable synthetic technique (31).

An additional advantage of the microwave-assisted method is the reduced consumption of reagents and solvents required to complete the reaction. Compared with the conventional reflux procedure, microwave irradiation allows the synthesis to be carried out using smaller quantities of reactants while maintaining excellent product yields. This feature not only lowers the overall cost of synthesis but also minimizes chemical waste and solvent

usage, making the process more consistent with the principles of green chemistry (32-35). The identity and purity of the synthesized compounds obtained from both synthetic routes were confirmed through spectroscopic characterization. Infrared (IR) and ^1H NMR spectra of the products synthesized by microwave irradiation were identical to those obtained using the conventional reflux method, indicating that microwave energy influences only the rate of the reaction and not the chemical structure of the final products (36). The characteristic absorption bands and proton resonances observed in the spectra were in excellent agreement with the proposed molecular structures, confirming the successful synthesis of the target sulfonylhydrazide derivatives. Overall, the present study demonstrates that microwave-assisted synthesis represents a highly efficient alternative to the conventional reflux method for the preparation of sulfonylhydrazide derivatives. The technique significantly reduces reaction time, increases product yield, decreases reagent and solvent consumption, and provides products with structural characteristics identical to those obtained by conventional synthesis (37, 38). These findings support the application of microwave-assisted organic synthesis as a reliable, economical, and environmentally friendly approach for the rapid synthesis of biologically important compounds.

CONCLUSION

The target compounds were successfully synthesized using both the conventional reflux method and microwave-assisted synthesis. A comparative evaluation of the two approaches demonstrated that microwave irradiation offers significant advantages over the conventional heating technique in terms of reaction efficiency, product yield, and operational simplicity. Microwave-assisted synthesis considerably reduced the reaction time while providing higher isolated yields of the desired compounds, confirming its effectiveness as an alternative synthetic strategy. The synthesized products obtained through microwave irradiation exhibited well-defined crystalline characteristics with sharp melting points, indicating their high purity. Furthermore, no

noticeable discoloration or impurity formation was observed in the reaction products synthesized under microwave conditions. The cleaner reaction profile may be attributed to rapid and uniform heating, which minimizes the occurrence of side reactions and thermal decomposition that are often associated with prolonged conventional reflux. Microwave irradiation promotes homogeneous heating throughout the reaction medium, allowing efficient molecular interactions between the reactants. This rapid and uniform energy transfer enables the reactants to overcome the activation energy barrier more effectively, resulting in faster reaction kinetics and improved conversion into the desired products. Consequently, the microwave-assisted method not only accelerates the synthesis but also enhances reaction selectivity and overall synthetic efficiency. Compared with the conventional reflux method, microwave-assisted synthesis requires shorter reaction times, lower energy consumption, and reduced solvent exposure, making it a more economical and environmentally sustainable approach. The simplified experimental procedure, together with reduced purification requirements and improved product recovery, further highlights the practical advantages of microwave-assisted organic synthesis for laboratory-scale and research applications. In summary, the present investigation demonstrates that microwave-assisted synthesis is a rapid, efficient, and reliable methodology for the preparation of *N'*-(2,4-dinitrophenyl)-4-methylbenzenesulfonylhydrazide derivatives. The method affords higher product yields, improved purity, reduced reaction times, lower energy requirements, and cleaner reaction profiles compared with the conventional reflux technique. These findings support the application of microwave-assisted synthesis as a green and cost-effective alternative for the synthesis of biologically important sulfonylhydrazide derivatives and provide a valuable platform for future medicinal chemistry and pharmaceutical research.

Acknowledgement

The author has no CONFLICT OF INTEREST about this manuscript.

Conflict of Interest

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REFERENCES

- [1] Wathey B, Tierney J, Lidström P, Westman J. The impact of microwave-assisted organic chemistry on drug discovery. *Drug discovery today*. 2002;7(6):373-80.
- [2] Dzierba CD, Combs AP. Microwave-assisted chemistry as a tool for drug discovery. *Annual Reports in Medicinal Chemistry*. 2002;37:247-56.
- [3] Arvela RK, Leadbeater NE. Rapid, easy cyanation of aryl bromides and chlorides using nickel salts in conjunction with microwave promotion. *The Journal of organic chemistry*. 2003;68(23):9122-5.
- [4] Crawford KR, Bur SK, Straub CS, Padwa A. Intramolecular cyclization reactions of 5-halo- and 5-nitro-substituted furans. *Organic letters*. 2003;5(18):3337-40.
- [5] Sondhi SM, Magan A, Sahu R, Mahesh VK, Shukla R, Patnaik GK. Evaluation of some anti-inflammatory pyrimidobenzimidazoles synthesized via novel tin (II) chloride-hydrochloric acid assisted water addition and reduction of 4, 4, 6-trimethyl-1-(2-nitroaryl)-1, 4-dihydropyrimidine-2 (3H)-thiones. *Synthesis*. 1994;1994(11):1175-80.
- [6] Khajavi MS, Rad-Moghadam K, Hazarkhani H. A facile synthesis of 6-substituted benzimidazo [1, 2-c]-quinazolines under microwave irradiation. *Synthetic communications*. 1999;29(15):2617-24.
- [7] Blackwell HE. Out of the oil bath and into the oven—microwave-assisted combinatorial chemistry heats up. *Organic & biomolecular chemistry*. 2003;1(8):1251-5.
- [8] M.H. Mahnashi, U. Rashid, H.H. Almasoudi, M.H. Nahari, I. Ahmad, A.S. Binshaya, O. Abdulaziz, M.A. Alsuwat, M.S. Jan, A. Sadiq, Modification of 4-(4-chlorothiophen-2-yl)thiazol-2-amine derivatives for the treatment of analgesia and inflammation: synthesis and in vitro, in vivo, and in silico studies, *Frontiers in Pharmacology*, 15 (2024) 1366695.
- [9] F. Mahmood, R. Ali, M.S. Jan, K.A. Chishti, S. Ahmad, A. Zeb, M. Ayaz, F. Ullah, M. Aasim, N.Z. Khan, Chemical characterization and analgesic potential of Notholirion thomsonianum extract, *Lat. Am. J. Pharm*, 38 (2019) 807-812.
- [10] Adam D. *Microwave chemistry: Out of the kitchen*. Nature Publishing Group; 2003.
- [11] Lipshutz BH, Frieman B. Microwave accelerated, Ni/C-catalyzed cross-couplings of in situ-derived zirconocenes. *Tetrahedron*. 2004;60(6):1309-16.
- [12] Mahajan K, Fahmi N, Singh RV. Synthesis, characterization and antimicrobial studies of Sb (III) complexes of substituted thioimines. 2007.
- [13] Kulisic T, Radonic A, Katalinic V, Milos M. Use of different methods for testing antioxidative activity of oregano essential oil. *Food chemistry*. 2004;85(4):633-40.
- [14] Sharma K, Singh R, Fahmi N, Singh R. Microwave assisted synthesis, characterization and biological evaluation of palladium and platinum complexes with azomethines. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*. 2010;75(1):422-7.
- [15] Mishra A, Tiwari A, Jain RK. Microwave induced synthesis and characterization of semiconducting 2-thiophenecarboxaldehyde metal complexes. *Advanced Material Letters*. 2012;3(3):213-9.
- [16] Bose AK, Manhas MS, Ganguly SN, Sharma AH, Banik BK. MORE chemistry for less pollution: Applications for process development. *Synthesis*. 2002;2002(11):1578-91.
- [17] Banik BK, Manhas MS, Newaz SN, Bose AK. Facile preparation of carbapenem synthons via microwave-induced rapid reaction. *Bioorganic & Medicinal Chemistry Letters*. 1993;3(11):2363-8.

- [18] M.H. Mahnashi, Y.S. Alqahtani, B.A. Alyami, A.O. Alqarni, M. Ahmed Alshrahili, M.A. Abou-Salim, M.N. Alqahtani, S. Mushtaq, A. Sadiq, M.S. Jan, GC-MS Analysis and Various In Vitro and In Vivo Pharmacological Potential of *Habenaria plantaginea* Lindl, Evidence-Based Complementary and Alternative Medicine, 2022 (2022) 7921408.
- [19] Bagley MC, Jenkins RL, Lubinu MC, Mason C, Wood R. A simple continuous flow microwave reactor. The Journal of organic chemistry. 2005;70(17):7003-6.
- [20] R. Zafar, H. Naureen, M. Zubair, K. Shahid, M. Saeed Jan, S. Akhtar, H. Ahmad, W. Waseem, A. Haider, S. Ali, Prospective application of two new pyridine-based Zinc (II) amide carboxylate in management of alzheimer's disease: Synthesis, characterization, computational and in vitro approaches, Drug Design, Development and Therapy, (2021) 2679-2694.
- [21] Comer E, Organ MG. A microreactor for microwave-assisted capillary (continuous flow) organic synthesis. Journal of the American Chemical Society. 2005;127(22):8160-7.
- [22] Chemat F, Esveld E. Microwave Super-Heated Boiling of Organic Liquids: Origin, Effect and Application. Chemical Engineering & Technology: Industrial Chemistry-Plant Equipment-Process Engineering-Biotechnology. 2001;24(7):735-44.
- [23] K. Ullah, S. Ali, A. Haider, S. Naz, S. Yousuf, K.S. Munawar, M.S. Jan, R. Zafar, R. Kumar, Investigation of pivalic acid-derived organotin (IV) carboxylates: Synthesis, structural insights, interaction with biomolecules, and computational studies, Journal of Molecular Structure, 1322 (2025) 140444.
- [24] A. Rauf, M. Ibrahim, T.S. Alomar, N. AlMasoud, A.A. Khalil, M. Khan, A. Khalid, M.S. Jan, D. Formanowicz, M.M. Quradha, Hypoglycemic, anti-inflammatory, and neuroprotective potentials of crude methanolic extract from *Acacia nilotica* L.-results of an in vitro study, Food Science & Nutrition, 12 (2024) 3483-3491.
- [25] Strauss CR, Trainor RW. Developments in microwave-assisted organic chemistry. Australian Journal of Chemistry. 1995;48(10):1665-92.
- [26] Zhu YJ, Wang WW, Qi RJ, Hu XL. Microwave-assisted synthesis of single-crystalline tellurium nanorods and nanowires in ionic liquids. Angewandte Chemie. 2004;116(11):1434-8.
- [27] Roberts BA, Strauss CR. Toward rapid, "green", predictable microwave-assisted synthesis. Accounts of chemical research. 2005;38(8):653-61.
- [28] M.S. Jan, M. Shahid, S. Ahmad, F. Hussain, A. Ahmad, F. Mahmood, U. Rashid, F. Ullah, N. Khan, M. Aasim, Synthesis of pyrrolidine-2, 5-dione based anti-inflammatory drug: in vitro COX-2, 5-LOX inhibition and in vivo anti-inflammatory studies, Latin Am J Pharm, 38 (2019) 2287-2294.
- [29] F. Mahmood, M.S. Jan, S. Ahmad, U. Rashid, M. Ayaz, F. Ullah, F. Hussain, A. Ahmad, A.-u. Khan, M. Aasim, Ethyl 3-oxo-2-(2, 5-dioxopyrrolidin-3-yl) butanoate derivatives: anthelmintic and cytotoxic potentials, antimicrobial, and docking studies, Frontiers in chemistry, 5 (2017) 119.
- [30] Makhluaf S, Dror R, Nitzan Y, Abramovich Y, Jelinek R, Gedanken A. Microwave-assisted synthesis of nanocrystalline MgO and its use as a bactericide. Advanced Functional Materials. 2005;15(10):1708-15.
- [31] Furniss BS. Vogel's textbook of practical organic chemistry: Pearson Education India; 1989.
- [32] Baxendale IR, Griffiths-Jones CM, Ley SV, Tranmer GK. Microwave-assisted Suzuki coupling reactions with an encapsulated palladium catalyst for batch and continuous-flow transformations. Chemistry-A European Journal. 2006;12(16):4407-16.

- [33] O.M. Alshehri, M.H. Mahnashi, A. Sadiq, R. Zafar, M.S. Jan, F. Ullah, M.A. Alshehri, S. Alshamrani, E.E. Hassan, Succinimide Derivatives as Antioxidant Anticholinesterases, Anti- α -Amylase, and Anti- α -Glucosidase: In Vitro and In Silico Approaches, Evidence-Based Complementary and Alternative Medicine, 2022 (2022) 6726438.
- [34] B. Waheed, S.M. Mukarram Shah, F. Hussain, M.I. Khan, A. Zeb, M.S. Jan, Synthesis, antioxidant, and antidiabetic activities of ketone derivatives of succinimide, Evidence-Based Complementary and Alternative Medicine, 2022 (2022) 1445604.
- [35] K. Shahzadi, S.M. Bukhari, A. Zaidi, T.A. Wani, M.S. Jan, S. Zargar, U. Rashid, U. Farooq, A. Khushal, S. Khan, Novel coumarin derivatives as potential urease inhibitors for kidney stone prevention and antiulcer therapy: from synthesis to in vivo evaluation, Pharmaceuticals, 16 (2023) 1552.
- [36] N. Masood, Q. Jamil, M.I. Aslam, M.I. Masood, J.H. Shirazi, Q.A. Jamil, M.S. Jan, B. Alsuwayt, A. Ahmad, S.M.A. Alnasser, Antioxidant, carbonic anhydrase inhibition and diuretic activity of *Leptadenia pyrotechnica* Forssk. Decne, Heliyon, 9 (2023).
- [37] Dubey R, Moorthy NSHN. Comparative studies on conventional and microwave assisted synthesis of benzimidazole and their 2-substituted derivative with the effect of salt form of reactant. Chemical and pharmaceutical bulletin. 2007;55(1):115-7.
- [38] Nüchter M, Ondruschka B, Bonrath W, Gum A. Microwave assisted synthesis—a critical technology overview. Green chemistry. 2004;6(3):128-41.