PREPARATION, BIOLOGICAL EVALUATION, AND APPLICATION OF THIADIAZOLE, SCHIFF BASE, AND TETRAZOLINE DERIVATIVES DERIVED FROM AQUEOUS *MORINGA* LEAF EXTRACTS: POM ANALYSIS FOR PHARMACOPHORE SITE IDENTIFICATION

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Abstract: *Moringa oleifera leaves have long been used in conventional medicine to treat a variety of ailments, including fever and sore throat. The close relationship between plants and human health has promoted the development of plant-based therapies, such as pharmaceuticals and nutritional supplements, thereby advancing traditional medicine and adding value to agriculture. In the present study, novel thiadiazole, Schiff base, and tetrazoline derivatives (H1, H2, and H3) were synthesized from nitrile-containing precursors obtained from the aqueous extract of Moringa oleifera leaves. The synthesis involved the reaction of the nitrile compound with thiourea in the presence of glacial acetic acid to form a heterocyclic thiadiazole intermediate, followed by condensation with an aromatic aldehyde to yield Schiff bases, and subsequent reaction with sodium azide to produce tetrazoline derivatives.*

The synthesized compounds were characterized by Fourier-transform infrared spectroscopy (FT-IR), melting point determination, and ^{1}H NMR spectroscopy. The biological activities of derivatives H1–H3 were evaluated against Staphylococcus aureus (Gram-positive), Escherichia coli (Gram-negative), and the fungal strain Candida albicans. Compared with standard drugs—ciprofloxacin for antibacterial activity and ketoconazole for antifungal activity—compound H3 exhibited superior antibacterial and antifungal activities. In addition, H3 demonstrated excellent antioxidant activity relative to ascorbic acid. POM analysis was further employed to identify promising pharmacophore sites within the synthesized compounds, highlighting their potential for pharmaceutical applications.

Keywords: *Nitril Compounds, thiourea, Schiff bases, cyclic addition reaction, tetrazoline, heterocyclic.*

Introduction

Moringa oleifera is an important medicinal plant rich in vitamins, minerals, flavonoids, and amino acids [1]. It belongs to the family Moringaceae and is a fast-growing tree that can reach heights of up to 10 m, characterized by its abundant green leaves [2]. Due to its wide availability and diverse phytochemical composition, *Moringa oleifera* has attracted considerable attention in medicinal and pharmaceutical research.

One of the primary objectives of organic synthesis is to develop efficient and sustainable synthetic routes to biologically active compounds using readily available starting materials. Among heterocyclic systems, 1,3,4-thiadiazole represents a five-membered heterocyclic scaffold with distinctive physicochemical properties. Its derivatives are well known for exhibiting a broad spectrum of biological activities, including antibacterial [3] and anti-Alzheimer effects [4,5]. Moreover, the 1,3,4-thiadiazole ring is an integral structural motif in several clinically used drugs, such as acetazolamide, methazolamide, cefazolin, cefazedone, sulfamethizole, and megazol [6].

Schiff bases constitute another important class of organic compounds due to their diverse biological activities, including antimalarial [7], antitumor [8], antifungal [9], antibacterial [10], antitubercular [11], antiviral [12], anticancer [13], and antiproliferative properties [14]. These compounds are typically formed through the condensation reaction of a primary amine with an aldehyde or ketone, often facilitated by catalysts such as glacial acetic acid. Structurally, Schiff bases are characterized by the presence of the azomethine (–C=N–) functional group, which plays a crucial role in their biological activity [15]. The field of synthetic organic chemistry continues to advance

the development of bioactive compounds, innovative drug designs, and efficient synthetic methodologies [16, 17]. Heterocyclic compounds have attracted particular attention because they constitute the structural core of numerous synthetic and naturally occurring medicinal agents [18, 19]. Among these, nitrogen-containing heterocycles are especially significant in the life sciences due to their structural diversity, ability to engage in intermolecular and enzyme interactions, electronic versatility, natural abundance, and widespread use as key intermediates in medicinal chemistry for the development of novel pharmaceuticals [20, 21].

Tetrazoles are an important class of heterocyclic compounds composed of a five-membered ring containing four nitrogen atoms and one carbon atom, and they can be obtained either by synthesis or from natural derivatives [22, 23]. The incorporation of the tetrazole moiety into bioactive molecules represents a rational strategy in drug design, as it can improve pharmacokinetic properties while reducing undesirable effects of potent drug candidates [24]. Cycloaddition reactions are among the most significant transformations in organic chemistry, owing to their synthetic utility and mechanistic importance [25].

In addition, by closely examining the effects of the most promising compounds on microbial cell membranes and evaluating their antioxidant properties, this study aims to gain deeper insight into their mechanisms of action. The findings are expected to contribute to the development of new and effective antimicrobial agents for the treatment of bacterial and fungal infections.

Experimental part

Materials. The chemicals used in this study were obtained from various commercial suppliers. Thiourea (99%) was purchased from Kem Aus, absolute ethanol (99%) from GCC, and glacial acetic acid, sodium azide, and aromatic amines were obtained from standard analytical suppliers. Dimethyl sulfoxide (DMSO, 99%) was supplied by BJH and used as the solvent.

Methods. Gas chromatography–mass spectrometry (GC–MS) analyses were performed using a PerkinElmer GC–MS system. Fourier-transform infrared (FT-IR) spectra were recorded on a Shimadzu 8400S spectrometer. Melting points were determined using a digital CG-1839-A0 melting point apparatus.

Synthesis of Thiadiazole Derivative 2-((2-(5-Amino-1,3,4-thiadiazol-2-yl)ethyl)(methyl)amino)-1-phenylpropan-1-ol (H1) [26]. The starting nitrile compound, 2-((1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)acetonitrile (0.005 mol, 0.012 g), was dissolved in 25 mL of ethanol. Thiourea (0.010 mol, 0.74 g) was added to the reaction mixture, followed by the dropwise addition of glacial acetic acid. The resulting mixture was refluxed for 12 h. After completion of the reaction, the mixture was cooled, filtered, and the crude product was recrystallized from ethanol to afford the thiadiazole derivative H1.

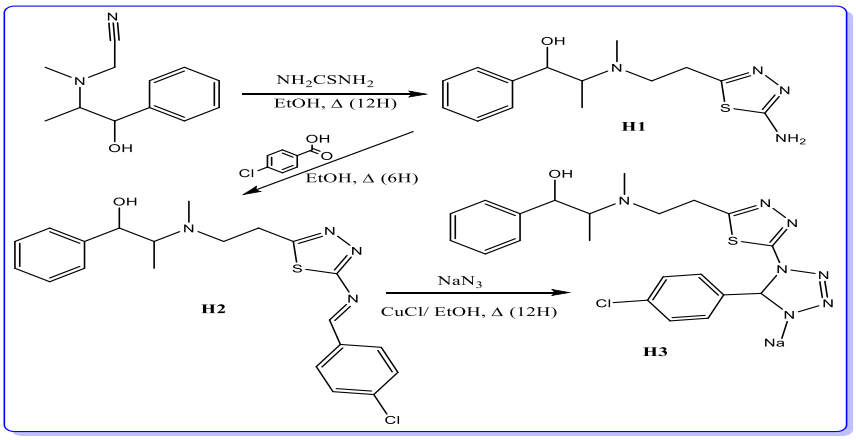
Synthesis of Schiff Base Derivative (Z)-2-((2-(5-((4-Chlorobenzylidene)amino)-1,3,4-thiadiazol-2-yl)ethyl)(methyl)amino)-1-phenylpropan-1-ol (H2) [27]. A mixture of thiadiazole compound H1 (0.001 mol, 0.292 g) and *p*-chlorobenzaldehyde (0.001 mol, 0.14 g) was dissolved in 20 mL of absolute ethanol. Several drops of glacial acetic acid were added as a catalyst, and the reaction mixture was refluxed for 6–8 h. Upon completion, the mixture was cooled and filtered, and the product was recrystallized from absolute ethanol to yield the Schiff base derivative H2.

Synthesis of Tetrazoline Derivative Sodium 5-(4-chlorophenyl)-4-(5-(2-((1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)ethyl)-1,3,4-thiadiazol-2-yl)-4,5-dihydrotetrazol-1-ide (H3) [27]. The tetrazoline derivative (H3) was synthesized by reacting the Schiff base derivative H2 (0.001 mol, 0.414 g) with sodium azide (NaN_3, 0.001 mol, 0.07 g) in dimethylformamide (DMF) as the solvent. Copper(I) chloride (CuCl) was added as a catalyst. The reaction mixture was stirred at room temperature for approximately 24 h. Upon completion, the reaction mixture was filtered, and the solid product was washed with distilled water, dried, and finally recrystallized from absolute ethanol to afford the tetrazoline compound H3.

Result and discussion

Due to their wide range of applications, particularly in pharmaceutical, industrial, and agricultural fields, heterocyclic compounds have attracted significant research interest. Accordingly, in this work, a series of heterocyclic derivatives—including thiadiazole, Schiff base, and tetrazoline compounds—were synthesized.

The thiadiazole derivative H1 was prepared through the reaction of a nitrile-containing compound, 2-((1-hydroxy-1-phenylpropan-2-yl)(methyl)amino)acetonitrile, with thiourea. The Schiff base derivative H2, namely (Z)-2-((2-(5-((4-chlorobenzylidene)amino)-1,3,4-thiadiazol-2-yl)ethyl)(methyl)amino)-1-phenylpropan-1-ol, was synthesized by the condensation reaction of compound H1 with an aromatic aldehyde. Subsequently, the tetrazoline derivative H3 was obtained via cycloaddition of the Schiff base H2 with sodium azide in the presence of copper(I) chloride as a catalyst. The overall synthetic route is illustrated in Scheme 1.

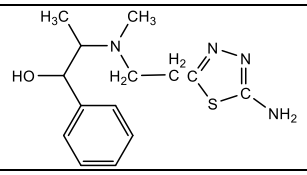
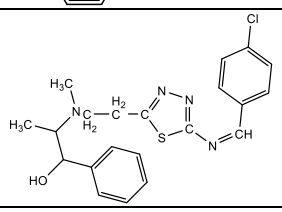


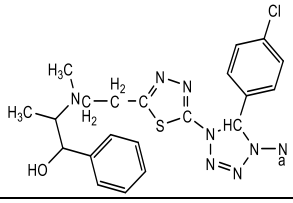
Scheme 1. Synthetic steps for preparation of derivatives[H_1],[H_2],[H_3]

The structural formulas, yields (%), melting points (Mp), colors, and FT-IR spectral data of the synthesized compounds are summarized in Table 1. Among the prepared derivatives, compound H3 exhibited the highest melting point (>250 °C), whereas the lowest melting point was observed for compound H2 (140–142 °C). The highest reaction yield was obtained for compound H3, while compound H1 showed the lowest yield.

In the FT-IR spectra (Fig.s 1-3), the characteristic absorption bands of the amino group (NH_2) appeared in the range 3284–3278 cm^{-1}, and the ν(C–S) stretching vibrations were observed at 630, 547, and 522 cm^{-1}. The Schiff base derivative H2 displayed a distinctive azomethine (C=N) stretching band at 1685 cm^{-1} [28]. Other characteristic absorption bands are listed in Table 1.

Table 1. Physicochemical properties and FT-IR spectral data (cm^{-1}) of the synthesized compounds H1, H2, and H3

Comp.	Structure of components	Mp, (°C)	Color	Yield %	V(C-H) aromatic	V(C-H) Aliphatic	Other bands
H1		165- 167	Thin white sheets	70	3105	2925-2856	NH_2:3384-3278 C-S:630 N-N(aromatic):1083 C=N:1467
H2		140-142	White powder	75	3095	2925-2852	N=CH:(imine)1685 C-Cl:761 C-S:547 N-N:(aromatic)1089

H3		248-250	Black powder	80	3130	2975-2925	C-S:522 C-Cl:775 N_3:2063 N=N(aromatic):1596

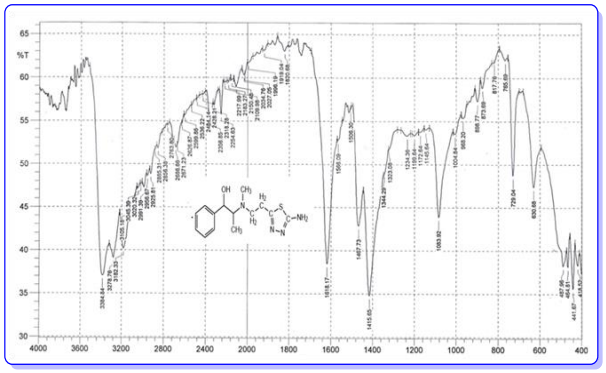


Fig. 1. FTIR spectrum of compound H1

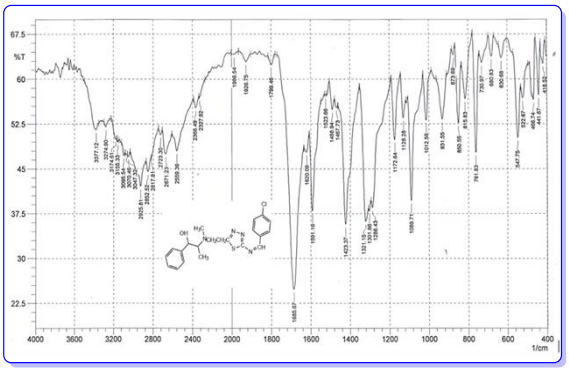


Fig. 2. FTIR spectrum of compound H2

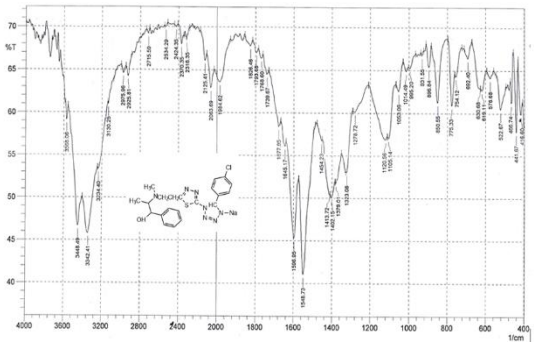


Fig. 3. FTIR spectrum of compound H3

The H-NMR spectrum of compound H1 (Fig. 4) explain chemical shifts, δ (ppm) showed 5.45 (s, H, NH_2), 3.26 (s, H, OH) , 1.24-1.51(d, 3H, $C\underline{H}_3$-CH), 2.29 (s, 3H, CH_3-N) 2.74-2.93(t, 4H, CH_2-CH_2), 3.14-3.87 (t, 1H, CH-N), 6.22-7.08 (m, 5H, Ar-H) [29].

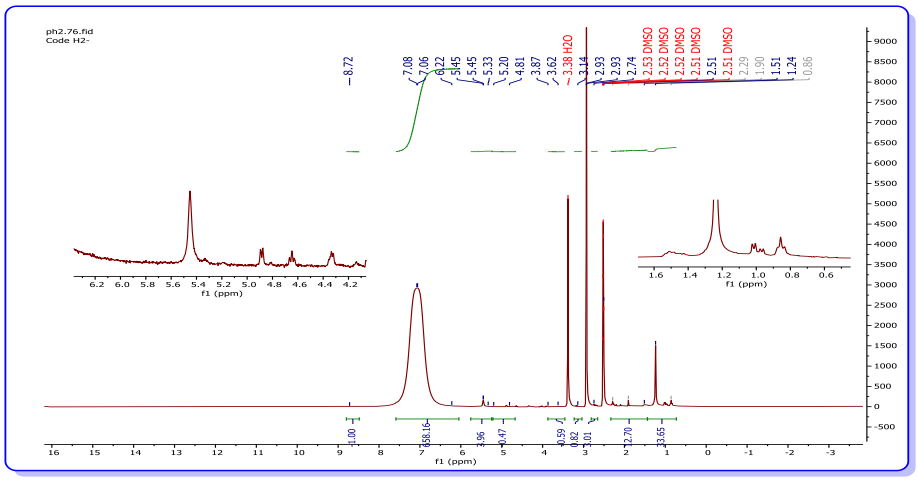


Fig. 4. ^{1}H-NMR spectra of compound H1

The ^{1}H-NMR spectrum of compound H2 (Fig. 5) explain chemical shifts, δ (ppm) showed 3.64 (s, H, OH), 1.25-1.52 (d, 3H, $C\underline{H}_3$-CH), 2.30 (s, 3H, CH_3-N) 2.32-2.90 (t, 4H, CH_2-CH_2), 3.13-3.33 (t, 1H, CH-N), 4.64-4.35 (d, 1H, CH-O), 6.78-7.72 (m, 9H, Ar-H), 9.68 (s, 1H, CH=N) [30].

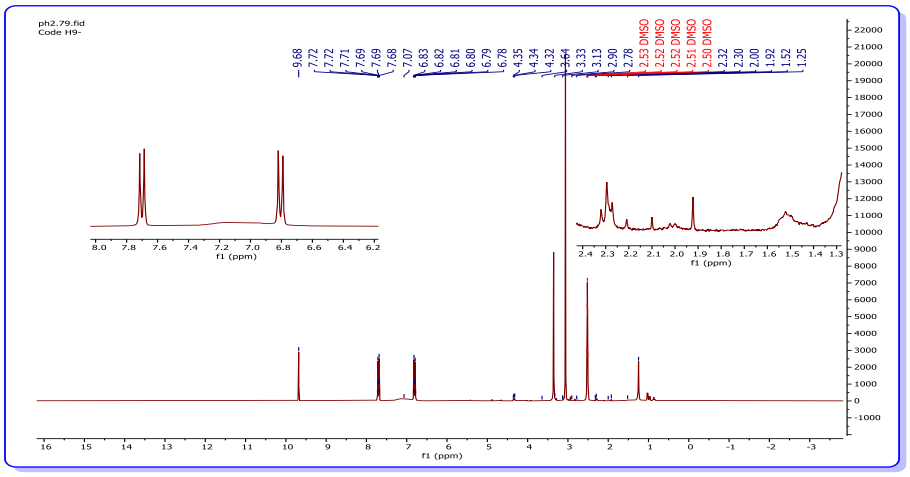


Fig. 5. ^{1}H-NMR spectra of compound H2

The Biological Activity Studies [31-34]. The biological activity of newly synthesized pharmaceutical compounds—namely thiadiazole, Schiff base, and tetrazoline derivatives (H1, H2, and H3)—prepared from a nitrile compound using *Moringa oleifera* leaf extract was investigated. These compounds were selected as the main bioactive components for antimicrobial evaluation.

Biological assays were carried out **in vitro** against two bacterial strains, *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative), as well as one fungal strain, *Candida albicans*. The antibacterial activity was evaluated using Mueller–Hinton agar, while antifungal activity was assessed using potato dextrose agar, due to their widespread application in medical microbiology.

Compound H1 exhibited moderate to weak antibacterial activity against the tested bacterial strains, whereas compound H3 showed a pronounced antibacterial effect, ranging from strong to moderate activity. The antibacterial activity data for all synthesized compounds are summarized in Table 2 and Fig. 6.

Table 2. Antibacterial activity of prepared compounds H1-H3

Compd.	***S.aureu***	***Escherichia coli***	***Candida albicans***
H1	13	11	15
H2	12	15	10
H3	27	13	15

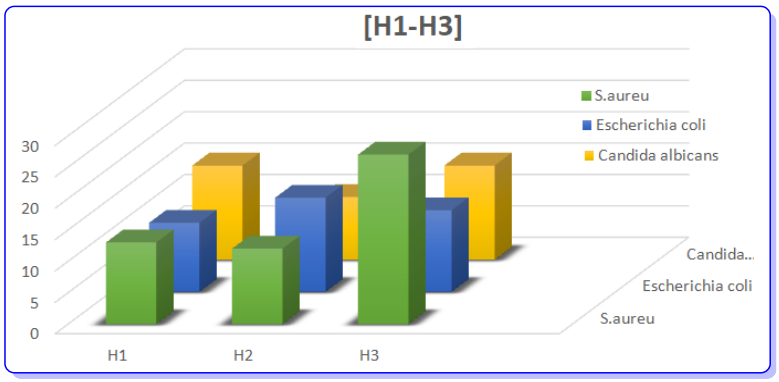


Fig. 6. Biological activity for synthesized compounds H1-H3

Antioxidant Studies [35, 36]. In this study, the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay was employed as a simple, inexpensive, and widely used method to evaluate the antioxidant activity of free radical–scavenging compounds. This method assesses the ability of substances to act as hydrogen donors or free radical scavengers.

The antioxidant activity of *Moringa oleifera* extract derivatives (H1, H2, and H3) was evaluated **in vitro** using the DPPH method. At a concentration of 0.5 µg/mL, compound H2 exhibited significantly lower antioxidant activity, whereas compound H3 showed the highest antioxidant activity among the tested compounds. Compound H1 displayed the lowest IC_{50} value (17.26 µg/mL), indicating the strongest radical-scavenging activity, while compound H2 showed a higher IC_{50} value (25.23 µg/mL). For comparison, the standard antioxidant ascorbic acid exhibited an IC_{50} value of 33.3 µg/mL.

The antioxidant activity of all compounds decreased with decreasing concentration. The antioxidant activity and IC_{50} values of the investigated compounds are summarized in Table 3.

Table 3. Antioxidants and IC50 for the derivatives (H1, H2, H3)

Compd.	Con.(ppm)	I (%)	IC50
H1	0.5	79.522	17.27
	0.25	68.645	
	0.125	52.114	
	0.0625	40.025	
H2	0.5	77.541	25.23
	0.25	65.541	
	0.125	42.521	
	0.0625	35.521	
H3	0.5	85.542	22.78
	0.25	72.212	
	0.125	59.854	
	0.0625	44.541	
Ascorbic acid	0.5	83.07	33.78
	0.25	65.92	
	0.125		
	0.0625		

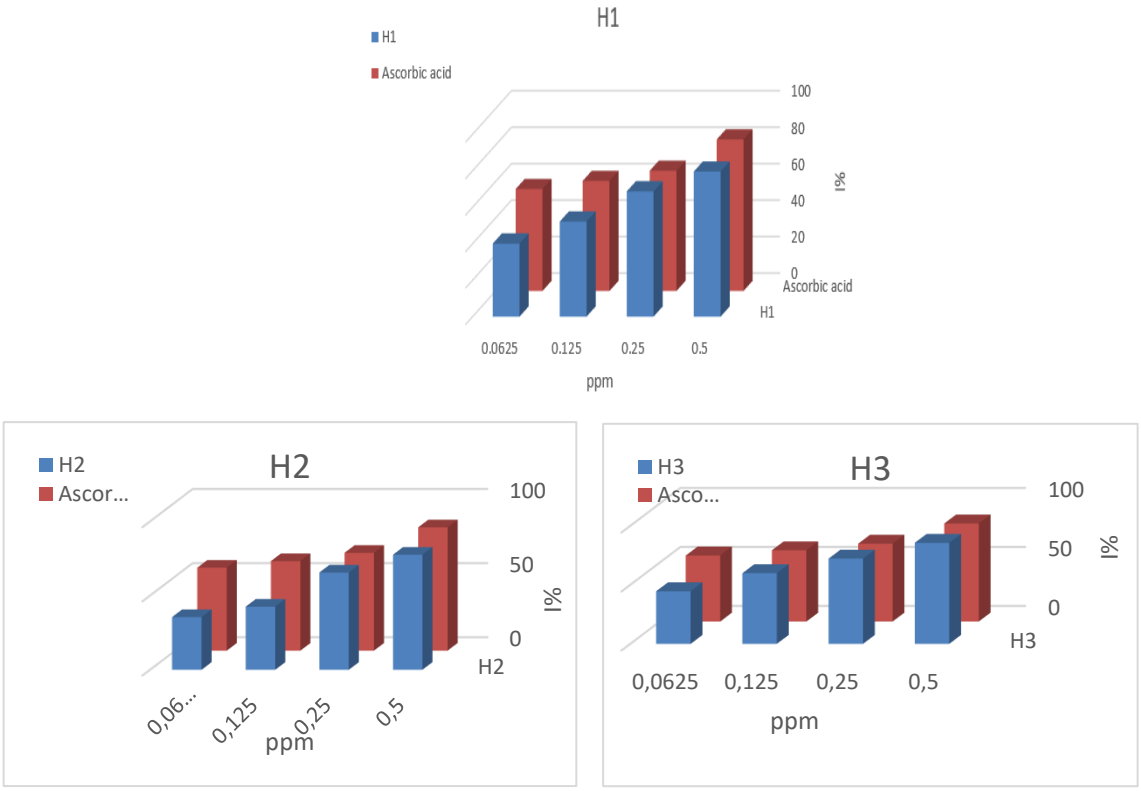


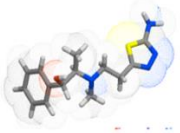
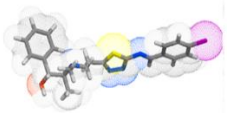
Fig. 7. The anti-oxidant studies for H1, H2 and H3

POM Theory (PETRA/OSIRIS/Molinspiration) [33–35]. The toxicity risks and molecular properties of compounds H1–H3 were evaluated using the PETRA, OSIRIS, and Molinspiration computational programs. OSIRIS analysis indicated that all investigated compounds possess favorable drug scores (DS = 63–93%) and are predicted to be non-mutagenic, non-tumorigenic, and non-toxic to reproductive systems.

Molinspiration analysis further revealed that compounds H1–H3 comply fully with Lipinski's rule of five, exhibit good drug-likeness, and show no rule violations. The predicted pharmacokinetic properties and drug-likeness probabilities of these compounds are summarized in Table 4.

POM analysis predicted that the physicochemical properties of the studied compounds enable effective antibacterial and antifungal activity, which is attributed to the presence of pharmacophoric sites such as $NH^{\delta+}$ and $S^{\delta-}$ groups. Compounds H1–H3 contain combined pharmacophore features, and their biological activity is influenced by the spatial distances between polar atoms ($NH^{\delta+}\cdots S^{\delta-}$), as presented in Table 4.

Table 4. Osiris and molinspiration calculations of molecular properties of (H1-H3)

No. Compd.	Structures	Osiris calculations	Molinspiration calculations
H1		Toxicity Risks: mutagenic, tumorigenic, irritant, reproductive effective; cLogP 1.02; Solubility -1.79; Molweight 292.0; TPSA 103.5; Druglikeness 8.94; Drug-Score 0.93	miLogP 1.22; MW 292.41; nON 5; nOHNH 3; nviolations 0; volume 270.32
H2		Toxicity Risks: mutagenic, tumorigenic, irritant, reproductive effective; cLogP 3.67; Solubility -3.99; Molweight 414.0; TPSA 89.95; Druglikeness 10.11; Drug-Score 0.67	miLogP 3.95; MW 414.96; nON 5; nOHNH 1; nviolations 0; volume 367.24
H3		Toxicity Risks: mutagenic, tumorigenic, irritant, reproductive effective; cLogP 3.88; Solubility -3.37; Molweight 479.0; TPSA 105.4; Druglikeness 8.07; Drug-Score 0.63	miLogP 0.57; MW 479.0; nON 8; nOHNH 1; nviolations 0; volume 391.40

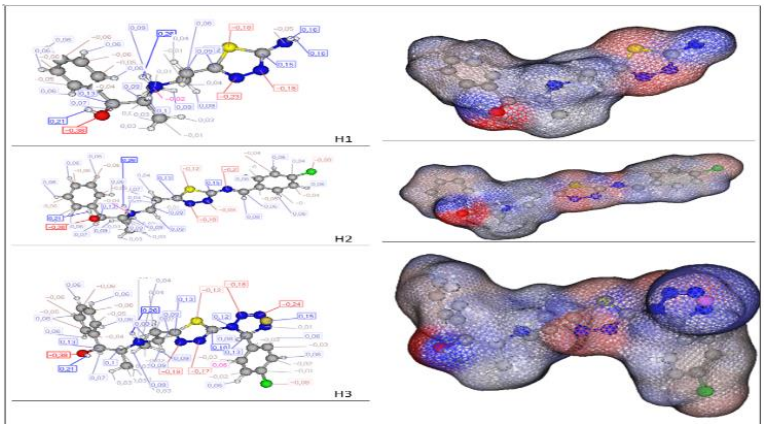


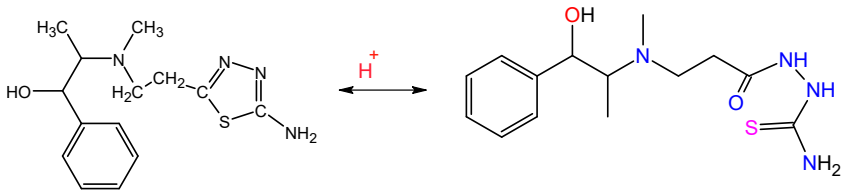
Fig. 10. Atomic Charge for components (H1-H3)

Conclusion

This study aimed to prepare an aqueous extract of *Moringa oleifera* leaves and to identify its active constituents under laboratory conditions. The most effective compounds were selected following investigation by gas chromatography–mass spectrometry (GC–MS). A nitrile compound was subsequently used as a precursor for the synthesis of thiadiazole, Schiff base, and tetrazoline derivatives (H1, H2, and H3). The structures of the synthesized compounds were confirmed using proton nuclear magnetic resonance (^1H NMR) and Fourier transform infrared (FTIR) spectroscopy.

The newly synthesized compounds were evaluated for their **in vitro** antibacterial, antifungal, and antioxidant activities. Several derivatives exhibited promising biological activity, with compound H3 showing the most pronounced antibacterial, antifungal, and antioxidant effects.

Moreover, a good correlation was observed between the experimental biological results and the computational studies based on POM analysis. The in silico evaluation indicated that the investigated heterocyclic compounds possess a favorable non-toxic profile, good bioavailability, and acceptable pharmacokinetic properties. These encouraging results support further investigation, particularly focusing on the possible metabolic pathways of the thiadiazole ring under acidic physiological conditions. The proposed metabolite structure is illustrated in Equation 1:



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