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Original Article

Synthesis and characterization of some thiazolidine 4-one derivatives derived from Schiff bases, and evaluation of their antibacterial and antifungal activity

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Abstract

Schiff bases compounds were synthesized by reaction of the Benzidine with different aldehydes and ketones by using microwave method to obtain compounds (N1-N5). Thiazolidine 4-one compounds were prepared by the cyclization of Schiff bases with thioglycolic acid to obtain thiazolidine 4-one compounds (N6-N10). The prepared compounds were characterized by physical methods, through melting points and color, as well as by spectroscopic methods such as FT-IR and ^{1}H-NMR. The purity of the prepared compounds was evaluated using TLC. The bioactivity of these compounds was tested on the growth of one type of a fungus of the yeast variety *Candida* was studied and type of bacterial isolates of *Bacillus pumilus* and the standard fungicide (Nystatin) of the fungus was used and the standard antibiotic (neomycin sulfate) of bacteria and the results indicate that the synthesized compounds have the ability to inhibit the fungus and bacteria used by using different concentrations. Molecular docking studies were conducted to examine how some of the synthesized compounds bind to the putative target, Protein structures i.e. HER2 (PDB ID: 1N8Z), Carcinoembryonic antigen (PDB ID; 2VER), BRCA1 (PDB ID 4OFB), BRCA2 (PDB ID 1MJE).

Keywords: Antibacterial activity, Antifungal activity, Benzidine, Schiff bases, Thiazolidine 4-one

1. Introduction

The condensation of a primary amine with a carbonyl molecule produces Schiff bases, which include an azomethine group (-CH=N-). Aliphatic aldehydes' Schiff bases are rather unstable and polymerizable, but aromatic aldehydes' Schiff bases, which have an effective conjugation mechanism, are more stable [1]. Preparative use, identification, detection, and determination of aldehydes or ketones, purification of carbonyl or amino compounds, or protection of these groups during complex or sensitive reactions are all applications of Schiff bases. In certain colours, they also serve as fundamental units. Schiff bases are bi- or tridentate ligands capable of producing exceptionally stable transition metal complexes. Some of these are used to make liquid crystals [2]. Schiff base reactions are useful in organic synthesis for forming carbon-nitrogen bonds Schiff bases appear to be a crucial step in a number of enzymatic processes involving the interaction of an enzyme with a substrate's amino or carbonyl group. The biochemical process, which includes the condensation of a primary amine in an enzyme, usually a lysine residue, with a carbonyl group of the substrate to generate an imine or Schiff base, is one of the most essential types of catalytic mechanisms [3].

Xanthine scaffold, in the form of methylxanthine alkaloids, is naturally found in coffee (Coffea arabica) and tea (Camellia sinensis) and is linked to a variety of biological functions, including bronchodilation (theophylline), diuretic (theobromine), and psychostimulant (caffeine) [4,5]. Chemical modification of this scaffold has led to the discovery of new biologically active molecules such as bronchodilators [5], hypoglycemiants [6], anticancer [7], and anti-inflammatory [8] agents. Linagliptin (Tradjenta, Trajenta), a DPP-4 inhibitor [9,10], is an example of a hypoglycemic medication that has been used in the United States for the treatment of diabetes mellitus type 2 since 2011. Its additional antioxidant capabilities have proven to be quite beneficial in the treatment of diabetic vascular problems (macrovascular-myocardial infarction, angina pectoris, stroke, and microvascular-diabetic nephropathy and retinopathy, impotence, and "diabetic foot") [11].

Many recent research studies have focused on the thiazolidine-4-one heterocycle because of its role in the synthesis [12] of new derivatives that have shown signifi-

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cant biological activity as antidiabetic [13, 14], antioxidant [15-17], anticonvulsant [18], anticancer [19], anti-inflammatory, analgesic [20], antimicrobial, antifungal [21], antiviral [22], antihypertensive, antiarrhythmic [23], Furthermore, the thiazolidinediones derived from this scaffold are essential medications for the treatment of type 2 diabetes. For diabetic mellitus treatment, three thiazolidinediones (pioglitazone, rosiglitazone, and lobeglitazone) have been licensed [23-26]. These medicines are quite efficient at lowering hyperglycemia, but they can have serious side effects such as hepatotoxicity, weight gain, retinal edema, and cardiovascular events [27, 28].

2. Materials and methods

2.1. Materials

The following chemicals were used in this study: Benzidine (CHMEC), 4-Hydroxybezaldehyde (Aldrich), 3,4-Dichlorobezaldehyde (Sigma- Aldrich), 3-Nitro-4-hydroxybezaldehyde (B.HD), Pyrrole-2-carboxybezaldehyde(Aldrich), 4-Hydroxy-3,5-dimethoxybezaldehyde (Merch), Absolute Ethanol (Supelco), Glacial Acetic Acid (Fluka), Benzene (Sigma - Aldrich), Thioglycolic acid (Aldrich).

2.2. Instrumentation

Unless otherwise stated, commercially accessible chemicals were used without further purification. Infrared (IR) spectra were acquired and calibrated using a polystyrene film on a Shimadzu FT-IR 8400S device, with m.p's not adjusted. The chemicals were discovered in potassium bromide disks (KBr). H-NMR spectra are acquired on 400 MHz AV III-HD-800 Bio. Spin spectrometer using dimethyl sulfoxide (DMSO.d^{-6}) as a solvent and tetramethylsilane (TMS) as an internal standard. Chemical changes were measured in parts per million. (ppm) downfield from TMS. The reaction was monitored and purity was checked using thin-layer chromatography (TLC). Microwave irradiations were performed in a modified domestic microwave oven, Universal - 850 watts, as seen in the images below.

2.3. Synthesis of Schiff base derivatives

2.3.1. General method

2.3.1.1. Synthesis of Schiff base derivatives

Benzidine (0.005 mole, 1g) was dissolved in 20 ml of ethanol and added 0.01 mole different bezaldehyde derivatives (4-hydroxy bezaldehyde, 3-nitro-4- hydroxybezaldehyde, 3,4-dichlorobezaldehyde, Pyrrole-2-carboxealdehyde, 4-hydroxe-3,5-dimethoxybezaldehyde) with stirring for 10 min at room temperature. The mixture added 5 drops of glacial acetic acid. The reaction mixture was refluxed in microwave for 4-7 minutes (850 watts). TLC (ethanol: hexane, 1:3 v/v) confirmed that the reaction was complete. The product was precipitated after the reaction mixture was cooled. The contents were filtered, and the result was washed twice with water before being dried and refined by recrystallization from ethanol (Fig. 1 and Table 1) [29].

2.4. Synthesis of thiazolidine- 4-one derivatives

2.4.1. General method

In dry benzene (10 ml), a combination of thioglycolic acid (0.002 mol) and Schiff base derivatives (0.001 mol) was stirred for 10 minutes. In the microwave, the reaction mixture was reheated for 4-7 minutes (200 watts). TLC was used to track the reaction's progress (Ethylacetate: Hexane 2:3). Solid product was formed in the reaction mixture after the reaction was completed, which was filtered, dried, and recrystallized from methanol (Fig. 2 and Table 2) [30].

3. Results

The Schiff base derivatives were synthesized by condensation of Benzidine with different aromatic aldehydes using glacial acetic acid as a ring-closing agent,

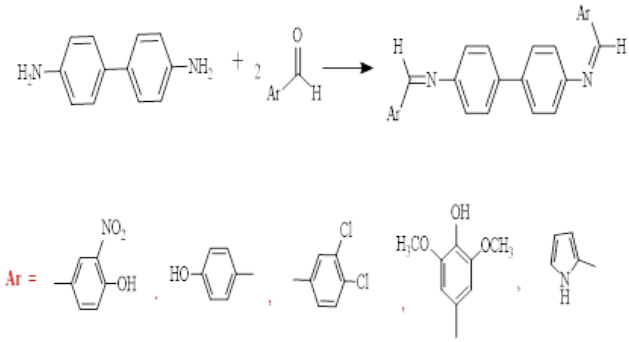


Fig. 1. Stipes of synthesis of Schiff base derivatives (N1-N5).

Table 1. Physical properties of the synthesized compounds (N1-N5).

Comp. No.	Molecular formula	Molecular weight	Color	M.P. ^{0}C	Time min	Yield %	R_f
N1	$C_{26}H_{18}N_4O_6$	482.45	Dark brown	150-152	6	77	0.22
N2	$C_{26}H_{20}N_2O_2$	392.46	Light brown	108-110	6	85	0.81
N3	$C_{26}H_{16}N_2Cl_4$	498.23	Yellow	99-100	7	82	0.85
N4	$C_{30}H_{24}N_2$	412.54	Light green	116-118	4	68	0.44
N5	$C_{22}H_{26}N_4$	346.48	Dark green	161-163	5	70	0.76

Table 2. Physical properties of the thiazolidine compounds (N6-N10).

Comp. No.	Molecular formula	Molecular weight	Color	M.P. ^{0}C	Time min	Yield %	R_f
N6	$C_{30}H_{22}N_4O_8S_2$	630.65	Yellow	150-152	8	65	0.36
N7	$C_{30}H_{24}N_2O_4S_2$	540.65	White	108-110	8	53	0. 71
N8	$C_{30}H_{20}Cl_4N_2O_2S_2$	646.42	White	99-100	9	62	0.75
N9	$C_{34}H_{28}N_2O_2S_2$	560.73	White	116-118	10	74	0.49
N10	$C_{26}H_{30}N_4O_2S_2$	494.67	Yellow	161-163	8	58	0.63

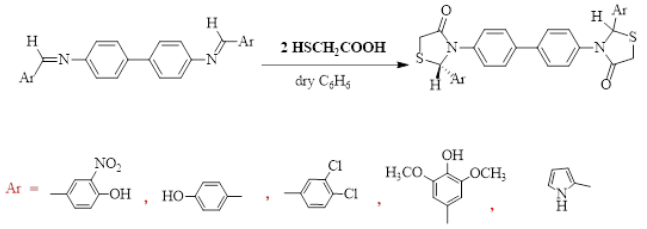


Fig. 2. Stipes of synthesis of thiazolidine derivatives (N6-N10).

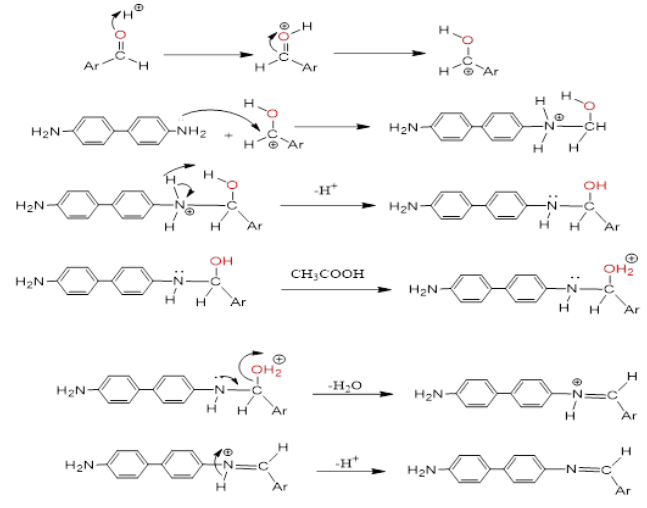


Fig. 3. Mechanism of the prepared compounds (N1-N5).

according to the mechanism shown in Fig. 3 [31].

The IR spectrum of compounds (N1-N5) showed the absence of a *v* ($2NH_2$) band and that showed band within (1585-1606 cm^{-1}) assigned to *v*(C=N), showed bands within (3012-3082 cm^{-1}) assigned to *v*(C-H) aromatic. Also showed two bands (1529-1599 cm^{-1}) and (1492-1532 cm^{-1}) assigned to *v*(C=C) aromatic showed other bands assigned to *v*(C-NO_2). The rest of the bands maintained their normal ranges, as shown in Table 3, which shows the results of infrared absorption of synthesis compounds (D_1-D_5) [29].

The 4-thiazolidine derivatives were synthesized by condensation of thioglycolic acid with different Schiff base derivatives using dry benzene as a ring-closing agent, according to the mechanism shown in Fig. 4 [32].

The IR spectrum of compounds (N5-N10) showed the absence of a *v* (C=N) band and that showed band within (1233-1280 cm^{-1}) assigned to *v*(C-N), showed bands within (3025-3098 cm^{-1}) assigned to *v*(C-H) aromatic. It also showed two bands (1575-1594 cm^{-1}) and (1470-140 cm^{-1}) assigned to *v*(C=C) aromatic. Showed other bands within (1645-1670 cm^{-1}) assigned to *v*(C=O), the rest of the bands maintained their normal ranges, as shown in Tables 4-6, which shows the results of infrared absorption of synthesis compounds (N5-N10).

3.1. *In-silico* docking studies

Molecular docking studies were performed using the AutoDock Vina 1.5.6 and Discovery Studio client version 4.0 was used to analyse the docking. Protein structures i.e. HER2 (PDB ID: 1N8Z), Carcinoembryonic antigen (PDB ID; 2VER), BRCA1 (PDB ID 4OFB), BRCA2 (PDB ID 1MJE) were obtained from the Protein Data Bank. ADT was used to remove water molecules and heteroatoms. Gasteiger charges were added to each atom, and the non-polar hydrogen atoms were merged. All torsions were allowed to rotate freely during docking and the grid map was centered at the active site of each protein and was adjusted to accommodate the binding site of each protein with a torsional degree of freedom of 0.5 units followed by calculation of grid energy using ADT. Docking was performed using a genetic algorithm with an initial population of 250 randomly placed individuals, a maximum number of 100,000 energy evaluations with a maximum number of interactions of 10,000. A docking run was performed for each ligand and receptor-ligand adduct for the lowest free energy of binding conformation from the largest cluster and saved in PDBQT format. The energy calculations

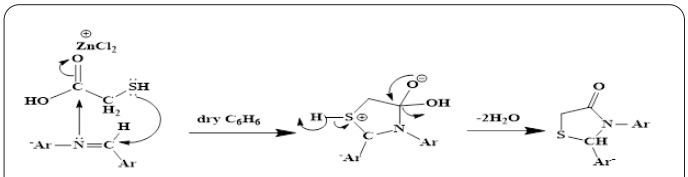


Fig. 4. Mechanism of the prepared compounds (N5-N10).

Table 3. FT-IR spectral data for compounds (N1-N5).

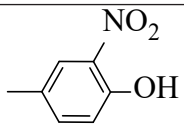
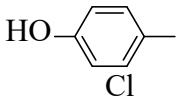
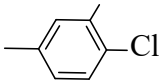
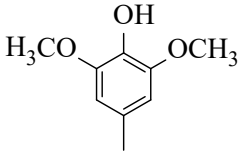
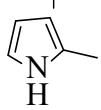
Comp. No.	Ar	ν(C-H) Ar cm^{-1}	ν(C=N) (cm^{-1})	ν(C=C) Ar cm^{-1}	ν others cm^{-1}
N1		3082	1585	1562-1521	$\nu(NO_2)_{sym,asym}$ 1336-1519
N2		3074	1593	1529-1492	ν(C-OH) 3347
N3		3014	1591	1540-1519	ν(C-Cl) 837
N4		3020	1589	1552-1526	ν(C-OH) 3382
N5		3012	1606	1599-1532	ν(N-H) 3269

Table 4. FT-IR spectral data for compounds (N6-N10).

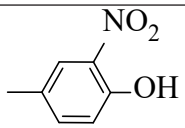
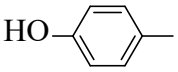
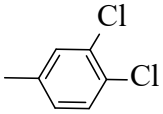
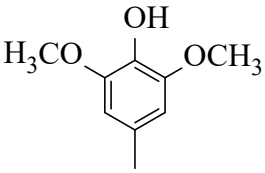
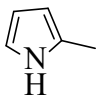
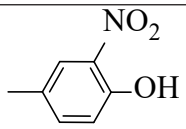
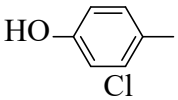
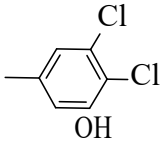
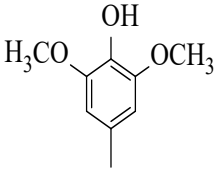
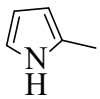
Comp. No.	Ar	IR (KBr) cm^{-1}						
		ν(C-H) Ar.	ν(C-H Aliph.	ν(C=O Lactam	ν (C=C) Ar.	ν (C-O)	ν (C-N)	Others
N6		3096	2948 2846	1670	1581 1487	1322	1255	ν (NO_2). *asy*.(1535) *sym*.(1402)
N7		3058	2977 2877	1650	1593 1483	1323	1274	ν(C-OH) 3372
N8		3036	2943 2865	1669	1594 1490	1339	1280	ν (C-Cl) 728
N9		3098	2920 2875	1660	1587 1470	1382	1264	ν(C-OH) 3343
N10		3025	2939 2856	1645	1575 1477	1361	1233	ν(N-H) 3259

Table 5. H^1-NMR data of the compounds (N1-N5).

Chemical shift (δ) ppm					
Comp. No.	Ar	δ (C-H) Ar.	δ (C-H) Methen	δ (O-H)	Others
N1		8.31-7.23	8.52	13.21	
N2		7.78-6.91	8.46	9.68	
N3		8.35-7.49	8.42	----	
N4		7.79-7.12	8.57	8.75	δ (CH_3) Aliph. 3.59
N5		7.78-7.4	8.51	----	δ (N-H) 11.21

were done using genetic algorithms. The resulting docked ligand conformation was analyzed in terms of energy, hydrogen bonding, and residue interaction between ligands and receptors to find the binding mode of the potent inhibitors. A detailed study of the ligand-receptor interactions was carried out and final coordinates of the ligand and receptor were saved. To display the interaction of the ligand with the receptor binding site, output was exported to Discovery Studio and protein-ligand interaction, active site binding residues and hydrogen bonds were analyzed. The free binding energy of the ligand with the proteins was obtained from the AutoDock Vina post-docking results, as shown in Tables 7-10 and Fig. 5-12, which show the results of docking of synthesis compounds.

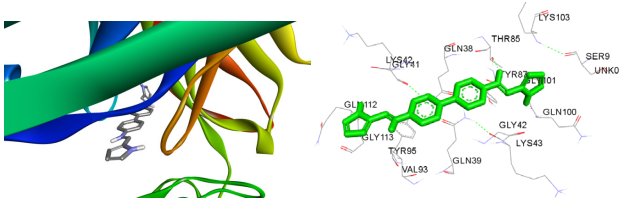


Fig. 5. HER2 binding interaction with compound N5.

3.2. Evaluation of the biological effectiveness of some synthesis compounds

The effect of some of the synthesis compounds on the growth of one type of a fungus of the yeast variety Candida was studied and the type of bacterial isolates of *B. pumilus* and the standard fungicide (Nystatin) of the fungus was used and the standard antibiotic (neomycin sulfate) of bacteria and the results indicate that the synthesized compounds have the ability to inhibit the fungus and bacteria used by using different concentrations of the concentrated compounds 5 mg/ml, 7 mg/ml, and 10 mg/ml compared with the inhibition with the standard antibodies with

Table 6. H^1-NMR data of the compounds (N6-N10).

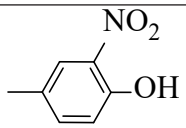
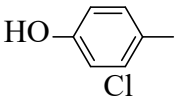
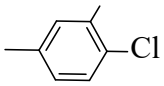
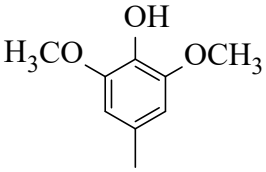
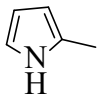
Comp. No.	Ar	Chemical shift (δ) ppm: δ (C-H) Ar.	δ (CH_2) Aliph.	δ (CH) Aliph	δ (O-H)	Others
N6		7.52-7.16	3.98-3.86	6.38	14.16	
N7		7.49-6.65	4.12-3.91	6.25	8.92	
N8		7.75-7.23	4.16-3.95	6.37	------	
N9		7.72-7.19	4.18-3.99	6.42	8.59	δ (CH_3) Aliph. 3.68
N10		7.69-7.21	4.11-3.93	5.86		δ (N-H) 11.49

Table 7. Summary of the docking scores and reported binding affinities of compounds with HER2 in the docking analysis with Autodock Vina Scoring functions.

Compound	Target	Binding Energy
compound-N5	HER2	-8.4
compound-N7	HER2	-8.4
Tamoxifen	HER2	-6.7

Table 8. Summary of the docking scores and reported binding affinities of compounds with Carcinoembryonic antigen in the docking analysis with Autodock Vina Scoring functions.

Compound	Target	Binding Energy
compound-N5	Carcinoembryonic antigen	-6.8
compound-N7	Carcinoembryonic antigen	-6.7
Tamoxifen	Carcinoembryonic antigen	-5.3

Table 9. Summary of the docking scores and reported binding affinities of compounds with BRCA1 in the docking analysis with Autodock Vina Scoring functions.

Compound	Target	Binding Energy
compound-N5	BRCA1	-7.1
compound-N7	BRCA1	-7.1
Tamoxifen	BRCA1	-6.6

Table 10. Summary of the docking scores and reported binding affinities of compounds with BRCA2 in the docking analysis with Autodock Vina Scoring functions.

Compound	Target	Binding Energy
compound-N5	BRCA2	-8
compound-N7	BRCA2	-8
Tamoxifen	BRCA2	-9.2

concentration 10 mg/ml, some synthesized compounds showed good inhibitory activity against bacteria and weak inhibitory activity against fungi [33, 34].

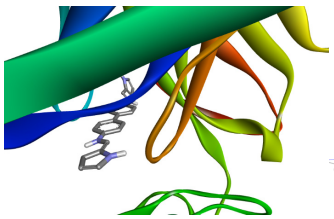


Fig. 6. HER2 binding interaction with compound N7.

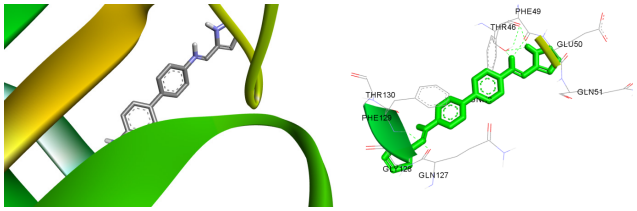


Fig. 7. Carcinoembryonic antigen binding interaction with compound N5.

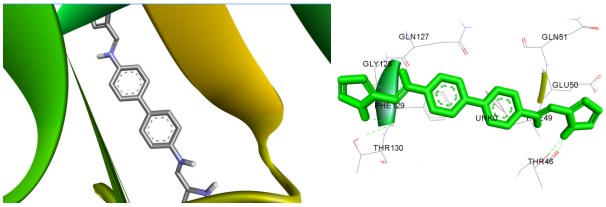


Fig. 8. Carcinoembryonic antigen binding interaction with compound N7.

3.3. Candida albicans Fungus

All synthesized compounds (N3, N5, N7, N9) showed weak activity at synthesized concentrations 5 mg/ml, 7 mg/ml, and 10 mg/ml, as in Table 11 and Fig. 13.

3.4. *Bacillus pumilus*

In these bacteria (*B. pumilus*) all compounds synthesized (N3, N5, N7, N9) showed good inhibitory activity at the concentrations 5 mg/ml, 7 mg/ml, and 10 mg/ml as

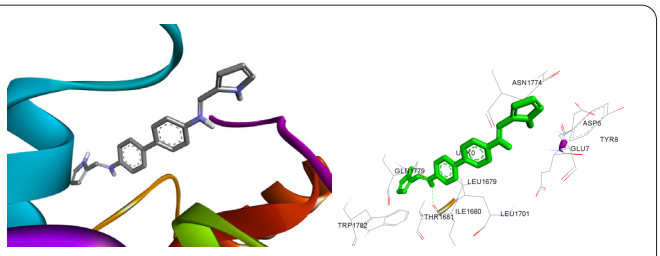


Fig. 9. BRCA1 binding interaction with compound N5.

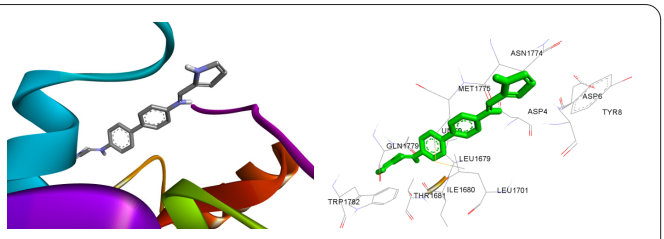


Fig. 10. BRCA1 binding interaction with compound N7.

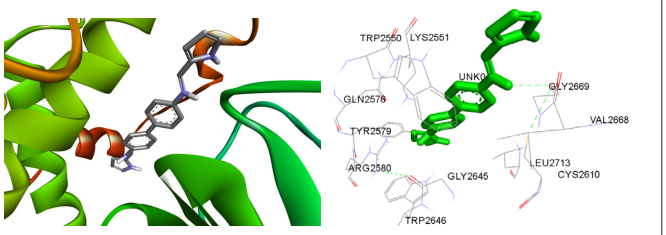


Fig. 11. BRCA2 binding interaction with compound N5.

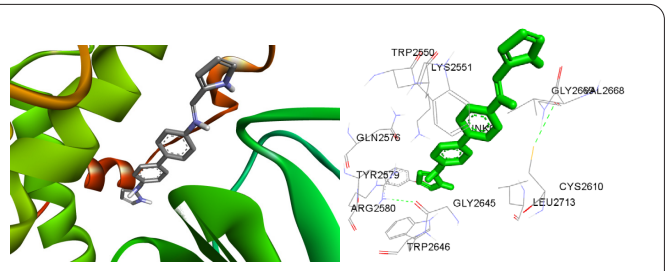


Fig. 12. BRCA2 binding interaction with compound N7.

Table 11. Antifungal activity of synthesized compounds (N3, N5, N7, N9).

Comp. No.	Standard 10 mg/ml	5 mg/ml	7 mg/ml	10 mg/ml
N3	32.5	15.4	15.6	15.7
N5	33.8	15.8	15.3	16
N7	33.5	14.6	14	15.5
N9	33	15.8	15.7	15.8

shown in Table 12 and Fig. 14.

4. Discussion

The synthesis of thiazolidine 4-one derivatives from Schiff bases marks a significant advancement in the development of novel antimicrobial agents. The successful characterization of these compounds through various spectroscopic techniques, including FT-IR and NMR, confirms the formation of the desired structures, as indicated by the characteristic absorption bands and chemical shifts observed in the spectra. The absence of specific vibrational modes, such as ν(C=N), in the thiazolidine derivatives, further supports the cyclization process that occurred during synthesis.

The synthesis of thiazolidine 4-one derivatives from Schiff bases is a notable achievement, particularly given the increasing demand for effective antimicrobial agents due to the rise of resistant pathogens. Previous studies have demonstrated that thiazolidine derivatives exhibit a range of biological activities, including antibacterial and antifungal properties. For example, a study by Trotsko [35] reported that thiazolidine-4-one derivatives synthesized from various aldehydes displayed significant antimicrobial activity against multiple bacterial strains, reinforcing the potential of these compounds as therapeutic agents.

The characterization methods employed—FT-IR and NMR—are well-established techniques in organic chemistry for confirming compound structures. In your findings, the characteristic absorption bands observed in

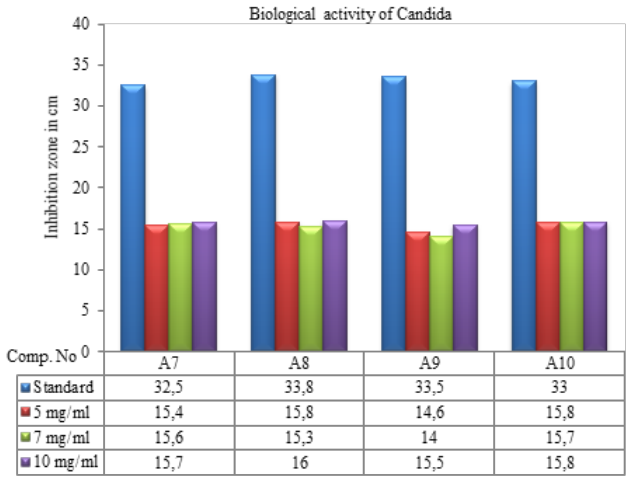


Fig. 13. Inhibitory activity of synthesized compounds (N3, N5, N7, N9) against Candida fungus.

Table 12. Antibacterial activity of synthesized compounds (N3, N5, N7, N9).

Comp. No.	Standard 10 mg/ml	5 mg/ml	7 mg/ml	10 mg/ml
N3	16.4	15.2	15.4	15.3
N5	18	17.1	17.2	17.9
N7	16.6	17.2	16.6	16.8
N9	17.6	14.1	15.7	15.8

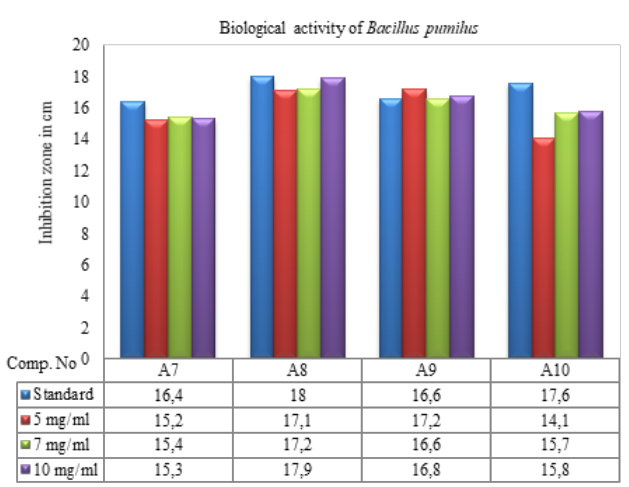


Fig. 14. Inhibitory activity of synthesized compounds (N3, N5, N7, N9) against *Bacillus pumilus.*

FT-IR spectra align with those reported in similar studies, where the successful formation of thiazolidine derivatives was confirmed through spectral analysis. The absence of the ν(C=N)ν(C=N) band is particularly significant, as it indicates successful cyclization—a critical step in confirming the formation of thiazolidine 4-one structures. This observation is consistent with findings from other research, where similar cyclization processes were corroborated by the disappearance of specific vibrational modes.

Additionally, your methodology utilizing microwave-assisted synthesis is supported by literature that highlights its advantages in enhancing reaction efficiency and yield. For instance, a review by Oliver Kappe [36] emphasizes how microwave irradiation can significantly reduce reaction times while improving product purity. This aligns with your results indicating high yields and purity levels for the synthesized compounds.

4.1. Antimicrobial activity assessment

The evaluation of antibacterial and antifungal activities revealed that certain thiazolidine derivatives exhibited substantial inhibitory effects against *B. pumilus* and *Candida* species. These findings are consistent with previous studies that have highlighted the efficacy of thiazolidine derivatives in combating microbial infections. The varying degrees of activity observed among different compounds may be attributed to structural differences that influence their interaction with microbial targets. For instance, modifications in functional groups can significantly alter lipophilicity and, consequently, membrane permeability, which is critical for antimicrobial action.

The significant antibacterial and antifungal activities demonstrated by your synthesized thiazolidine derivatives against *B. pumilus* and *Candida* species align with findings from multiple studies that have reported similar efficacy of thiazolidine derivatives in microbial inhibition. For example, a study by Trotsko [35] showed that specific thiazolidine-4-one derivatives exhibited potent antimicrobial activity against various bacterial strains, including *Bacillus* species, supporting the notion that these compounds are promising candidates for further development as therapeutic agents.

The structural variations among the synthesized compounds likely play a crucial role in their differing levels of antimicrobial activity. Research has indicated that modifications in functional groups can significantly affect the lipophilicity of compounds, which in turn influences their ability to permeate microbial membranes. A study by Viji et al. [37] highlighted how altering substituents on thiazolidine derivatives affected their antimicrobial potency, emphasizing the importance of optimizing these structural features to enhance efficacy.

Moreover, the relationship between lipophilicity and membrane permeability is well-documented in pharmacology. Compounds with higher lipophilicity tend to exhibit better membrane penetration, which is essential for achieving effective intracellular concentrations necessary for antimicrobial action. This underscores the need for further exploration into the structure-activity relationships (SAR) of thiazolidine derivatives to identify optimal modifications that maximize their therapeutic potential.

4.2. Molecular docking insights

Molecular docking studies provided valuable insights into the binding affinities of these compounds with target proteins such as HER2, BRCA1, and BRCA2. The binding energies obtained from AutoDock Vina suggest that compounds N5 and N7 have strong interactions with these targets, indicating their potential as lead compounds for further drug development. The observed docking scores are comparable to those of known inhibitors like Tamoxifen, underscoring the therapeutic potential of thiazolidine derivatives in cancer treatment. Future studies should focus on elucidating the precise mechanisms of action through in vitro and in vivo assays to validate these computational predictions.

The molecular docking results indicating strong binding affinities of thiazolidine derivatives N5 and N7 with key oncogenic targets such as HER2, BRCA1, and BRCA2 highlight their potential as promising candidates for anticancer drug development. This is particularly relevant given the critical roles these proteins play in cancer progression and treatment resistance. Previous research has similarly identified thiazolidine derivatives as having significant anticancer activity. For instance, a study by Sharma et al. [38] reported that thiazolidine-4-one derivatives exhibited potent cytotoxic effects against various cancer cell lines, reinforcing the therapeutic promise of this chemical class.

The binding energies calculated using AutoDock Vina suggest that compounds N5 and N7 have comparable or even superior interactions with these targets compared to Tamoxifen, a well-known therapeutic agent for breast cancer. This comparison is notable because it indicates that these thiazolidine derivatives could serve as effective alternatives or adjuncts to existing therapies. Research by Tilekar et al. [39] supports this notion, demonstrating that modifications in thiazolidine structures can enhance binding affinities to similar targets, thereby improving their efficacy as anticancer agents.

Moreover, your recommendation for future studies to elucidate the mechanisms of action through in vitro and in vivo assays is crucial for validating the computational predictions made in this study. A comprehensive understanding of how these compounds interact at the molecular level will provide insights into their pharmacodynamics and potential side effects. This approach aligns with current trends in drug discovery, where computational methods are increasingly integrated with experimental validation to streamline the development of new therapeutics.

4.3. Implications for future research

The findings from this study pave the way for further exploration into the structure-activity relationships (SAR) of thiazolidine derivatives. By systematically modifying substituents on the thiazolidine ring, researchers can optimize antimicrobial efficacy while minimizing potential side effects. Additionally, exploring the synergistic effects of these compounds when used in combination with existing antibiotics could enhance therapeutic outcomes against resistant strains.

The emphasis on exploring the structure-activity relationships (SAR) of thiazolidine derivatives is crucial for advancing their development as effective antimicrobial agents. This approach allows researchers to identify which structural modifications lead to enhanced biological activity while also considering safety profiles. Previous studies have demonstrated that systematic modifications of

thiazolidine derivatives can significantly impact their antimicrobial properties. For example, research by Stana et al. [40] highlighted how specific substitutions on the thiazolidine ring improved antibacterial activity against various pathogens, indicating that careful design can lead to more potent compounds.

The potential for optimizing antimicrobial efficacy while minimizing side effects is particularly relevant in light of the growing concern over antibiotic resistance. The exploration of synergistic effects when combining these thiazolidine derivatives with existing antibiotics is a promising strategy to combat resistant strains. A study by Trotsko et al. [41] showed that certain thiazolidine derivatives, when used in combination with standard antibiotics, exhibited enhanced antibacterial activity, suggesting that such combinations could be a viable approach to overcoming resistance mechanisms.

Furthermore, the ability to modify substituents on the thiazolidine ring opens up avenues for developing compounds with dual-action mechanisms, targeting both bacterial and fungal infections simultaneously. This is particularly important given the increasing incidence of co-infections in clinical settings, where patients may be affected by multiple pathogens. Future studies should focus on not only optimizing individual compound structures but also investigating the pharmacokinetics and pharmacodynamics of these combinations to ensure effective therapeutic outcomes.

Moreover, expanding the scope of biological testing to include other pathogens could provide a broader understanding of the applicability of these compounds in clinical settings. Investigating their safety profiles through cytotoxicity assays will also be essential before advancing to clinical trials.

The suggestion to expand biological testing to include a wider range of pathogens is critical for assessing the full potential of thiazolidine derivatives as antimicrobial agents. This approach aligns with current trends in drug discovery, where broad-spectrum activity is highly sought after due to the increasing incidence of multi-drug resistant infections. Previous studies have shown that certain thiazolidine derivatives exhibit activity against various pathogens beyond those initially tested. For example, research by Khamitova et al. [42] demonstrated that thiazolidine derivatives not only inhibited *B. pumilus* and *Candida* species but also showed promising activity against other bacterial strains, suggesting their potential as broad-spectrum antimicrobials.

Furthermore, the importance of investigating safety profiles through cytotoxicity assays cannot be overstated. A thorough evaluation of the safety and toxicity of new compounds is essential prior to clinical trials, as it ensures that any potential adverse effects are identified early in the development process. Studies such as those conducted by Trotsko [35] have highlighted the necessity of cytotoxicity assessments in evaluating the therapeutic index of new antimicrobial agents. Their findings indicated that while some thiazolidine derivatives exhibited strong antimicrobial activity, they also demonstrated varying levels of cytotoxicity against human cell lines, necessitating careful optimization of compound structures to balance efficacy and safety.

Incorporating these additional testing parameters will not only enhance the understanding of the therapeutic potential of thiazolidine derivatives but also align with regulatory requirements for drug development, ultimately facilitating a smoother transition from laboratory research to clinical application.

5. Conclusion

The study presents the synthesis and characterization of thiazolidine 4-one derivatives derived from Schiff bases, highlighting their potential as antibacterial and antifungal agents. The compounds were synthesized through a microwave-assisted method, demonstrating efficient yields and purity verified by TLC and spectroscopic techniques such as FT-IR and NMR. Biological evaluation revealed that certain derivatives exhibited significant inhibitory effects against *Bacillus pumilus* and *Candida* species, suggesting their potential application in treating microbial infections. Additionally, molecular docking studies indicated favorable binding interactions with key proteins associated with cancer, further supporting the therapeutic potential of these compounds. Overall, this research underscores the promising role of thiazolidine derivatives in drug development for both antimicrobial and anticancer applications. In conclusion, this study not only demonstrates the successful synthesis and characterization of novel thiazolidine 4-one derivatives but also highlights their promising biological activities. Continued research in this area could lead to significant advancements in antimicrobial therapy.

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