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Synthesis, and Biological Activities of Some Schiff Bases Derivatives

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ABSTRACT

Objective: *This study aims to synthesize and evaluate the biological activities of four Schiff base compounds derived from the condensation of benzaldehyde and selected amine derivatives, with a focus on determining their anticancer, antibacterial, and antifungal potentials.* ***Method:*** *Four compounds—namely compound 1 [(E)-1-(4-chlorophenyl)-N-(6-methoxybenzo[d]thiazol-2-yl)methanimine], compound 2 [(E)-4-(((6-methoxybenzo[d]thiazol-2-yl)imino)methyl)phenol], compound 3 [(E)-5-((2-methylbenzylidene)amino)-2,3-dihydrophthalazine-1,4-dione], and compound 4 [(E)-5-((2-hydroxybenzylidene)amino)-2,3-dihydrophthalazine-1,4-dione]—were synthesized and subjected to in vitro screening.* ***Results:*** *Compound 1 exhibited the strongest anticancer activity, outperforming the other derivatives. Compounds 1 and 2 showed pronounced antibacterial effects against Staphylococcus aureus, while compound 4 demonstrated activity against Escherichia coli. Compounds 3 and 4 also displayed significant antifungal inhibition against Candida albicans.* ***Novelty:*** *The study identifies specific structure–activity relationships among newly synthesized Schiff bases, highlighting distinct bioactive profiles and offering promising lead compounds for future therapeutic development.*

INTRODUCTION

Schiff bases are compounds composed of carbon and nitrogen atoms, which alkyl or aryl substituents can be combined [1]. Last years, numerous reports have investigated Schiff bases with biological properties, such as antifungal, antibacterial, anticancer, etc. The main property of Schiff bases is high purity and yield [2], [3].

Schiff bases have long served as a source of inspiration for chemists and biochemists [4]. Schiff bases are utilized in a variety of applications, including catalytic processes, crystal engineering, photo- or chemo detectors in biological systems, and medicine [5]. The Schiff base derivatives are important because of their biological activities [6].

Many derivatives of Schiff bases are reported, and their merged together will resultant a sum of exceedingly suitable molecules with appropriate biological activities [7,8]. Schiff bases and their derivatives, can inhibit cancer cells and induce cell death, requiring further investigation to determine their potential [9], [11].

The availability of pharmacophore fragments and a biodegradable and non-toxic Schiff bases allows for the creation of drugs carriers with their own potential pharmacological, opening up new avenues for further inquiry [12]. Herein, seek to prepare Schiff bases derivatives with perspective significance of biological properties.

RESEARCH METHOD

All of the chemical materials supplied from Sigma Aldrich (99.8%). Deuterated solvents and tetramethylsilane (TMS) as an internal standard. The chemical shifts were measured in (δ) ppm using a Bruker DRX-500 spectrometer at 500 MHz and 125 MHz respectively for ^{1}H-NMR analysis.

FT-IR-1600 Perkin-Elmer spectrophotometer. Mass spectrum using an Agilent Technologies 5975C Spectrometer with EI at 70 eV.

Synthetic procedures [13-18]

Compound 1 (*E*)-1-(4-chlorophenyl)-N-(6-methoxybenzo[*d*]thiazol-2-yl)methanimine

A mixed solution of 4- ethoxybenzaldehyd (0.005 mol), 25 mL of ethanol, glacial acetic acid (3 drops), and 2-amino-6-methoxybenzothiazole (0.005 mol) were added in a round flask. 5 hours of reflux under room temperature. The filtration, and air-dried overnight to obtain a solid product. The yield 72%, light yellow-orange, and the melting point was 132 -134 °C**;** MS (ESI) m/z =312.39 [M].

Compound 2 (*E*)-4-(((6- methoxybenzo[*d*]thiazol-2-yl)imino)methyl)phenol

A mixed solution of 4-hydroxybenzaldehyd (0.005 mol), 25 mL of ethanol, glacial acetic acid (3 drops), and 2-amino-6-methoxybenzothiazole (0.005 mol) were added in a round flask. 5 hours of reflux under room temperature. The filtration, and air-dried overnight to obtain a solid product. The yield 80%, light orange, and the melting point was 234-236 °C. MS (ESI) m/z = 284.33 [M].

Compound 3 (*E*)-5-((2- methylbenzylidene)amino)-2,3-dihydrophthalazine-1,4-dione

A mixed solution of 4-methylbenzaldehyd (0.005 mol), 25 mL of ethanol, glacial acetic acid (3 drops), and 3 - aminophthalhydrazide (0.005 mol), were added to in a round flask. 5 hours of reflux under room temperature. The filtration, and air-dried overnight to obtain a solid product. The yield 77%, yellow, and the melting point was 97-99 °C. MS (ESI) m/z = 279.30 [M+1].

Compound 4 (*E*)-5-((2- hydroxybenzylidene)amino)-2,3-dihydrophthalazine-1,4-dione

A mixed solution of 2-hydroxybenzaldehyd (0.005 mol), 25 mL of ethanol, glacial acetic acid (3 drops), and 3 - aminophthalhydrazide (0.005 mol), were added in a round flask. 5 hours of reflux under room temperature. The filtration, and air-dried overnight to obtain a solid product. The yield 80%, yellow, and the melting point was 111-113 °C. MS (ESI) m/z = 281.27 [M+1].

Anticancer method

The compounds' anticancer activity was evaluated using MDA-MB-231 cancer cells. 96-well plate of 1×10^4 cells/well was incubated overnight in RPMI-1640 media with 10% fetal bovine serum and 1% penicillin-streptomycin at 37 °C in a humidified environment with 5% CO_2. DMSO used to prepare concentrations of compounds via serially diluted to reach their final concentrations. After 48 hours of treatment, 28 µL of MTT solution (5 mg/mL) was added to each well, and incubated for 2 hours. the formazan crystals were dissolved in 100 µL of DMSO and use a microplate reader (BioTek ELx800) at 570 nm [19].

Antibacterial method

Minimum inhibitory concentrations (MICs) were estimated using the diffusion method against *Escherichia coli* ATCC 11775 and *Staphylococcus aureus* ATCC 12600. In brief, applied a different concentration to each Petri dish (7 mm diameter holes in the agar gel spaced 20 mm apart). The Petri plates were incubated for 24 hours at 36±1 ^{o}C in aerobic conditions. Then, the growth of bacterial was monitored to determine the MIC values [20].

Antifungal method

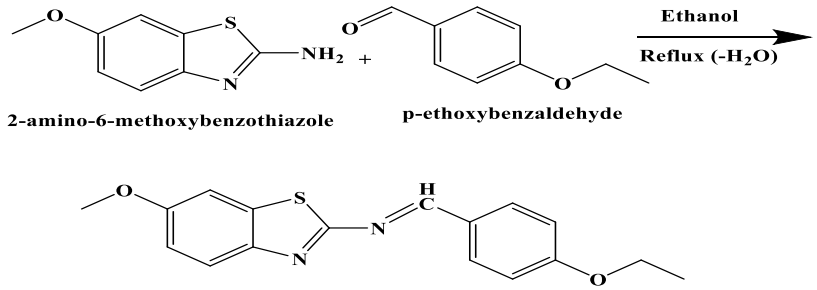
A standardized 10^6 conidia/mL by sterile saline solution (0.85%) of fungal suspension (*Candida albicans*), and 100 µl fungal suspension was added to each Petri dish. 10 minutes later, different concentrations of compounds were prepared in 6-mm diameter holes. 70 % Dimethyl sulfoxide (DMSO) as positive control, and the fungicide tebuconazole (TEB) (Folicur 20EC) was employed at 0.1%. The plates were incubated at 28 ± 2 °C, and the experiment repeated three times. After 72 hours, we measured the diameter of inhibition, and the zones of inhibition were estimated [21].

Statistical analysis

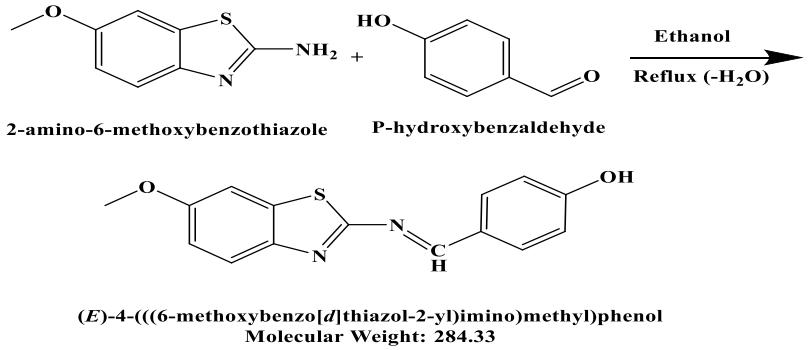
The IC_{50} is calculated using the excel file's amount response curve. All absorbances at 570 nm are recorded for each concentration. The absorbance values are used to calculate the percentage of viability for each concentration. Next, the standard deviation and average viability are calculated. IC_{50} was calculated by replacing y in the equation with 50, which represents 50% viability, and computing the x value at y=50 to determine IC_{50} concentration

RESULTS AND DISCUSSION

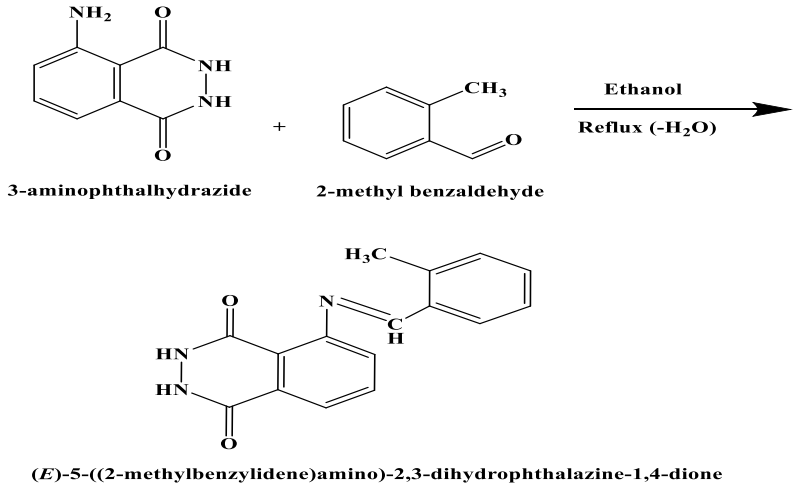
The Schiff bases derivatives (compound **1** [(*E*)-1-(4-chlorophenyl)-N-(6-methoxybenzo[*d*]thiazol-2-yl)methanimine], compound **2** [(*E*)-4-(((6-methoxybenzo[*d*]thiazol-2-yl)imino)methyl)phenol], compound **3** [(*E*)-5-((2-methylbenzylidene)amino)-2,3-dihydrophthalazine-1,4-dione], and compound 4 [(*E*)-5-((2- hydroxybenzylidene)amino)-2,3-dihydrophthalazine-1,4-dione]) were synthesized by condensation of 4- ethoxybenzaldehyd, 4-hydroxybenzaldehyd, 4-methylbenzaldehyd, and 2-hydroxybenzaldehyd with 2-amino - 6-methoxybenzothiazole and 3 - aminophthalhydrazide, as shown in **Scheme 1-4.** FT-IR, ^{1}H-NMR, and Mass spectrum were used to identify the right chemical structure of the Schiff bases.



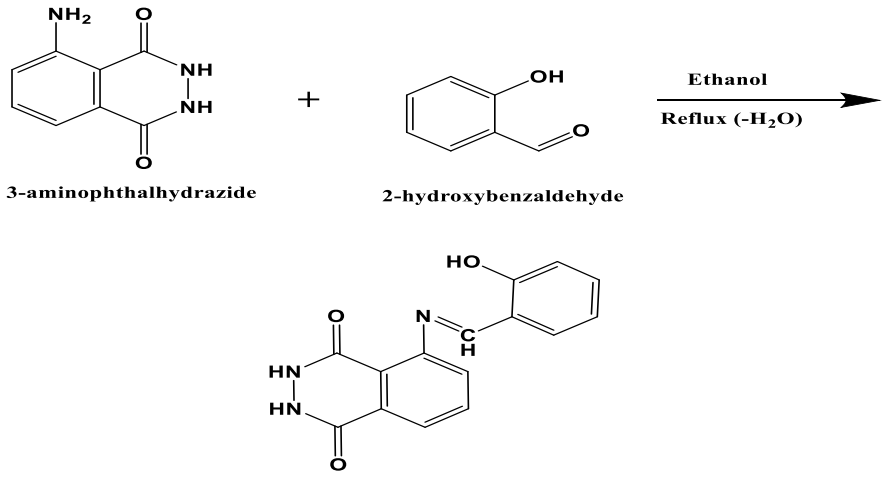
Scheme 1. The synthesis reaction of compound 1.



Scheme 2. The synthesis reaction of compound 2.



Scheme 3. The synthesis reaction of compound 3.



Scheme 4. The synthesis reaction of compound 4.

Figure 1, showed FT-IR bands of the compound 1 (HC=N stretching (1598.20 cm^{-1}), C-H aromatic (3000.29 cm^{-1}), S-H stretching (2366.27 cm^{-1}), N-H stretching (3389.88 cm^{-1}), O-CH_3 stretching (1420.41 cm^{-1}), CH_3 stretching (2926.15 cm^{-1}), O-C_2H_5 (2850.58 cm^{-1}) stretching, and C=C stretching (1558.89 cm^{-1}). **Figure** 2, showed ^{1}H-NMR analysis of compound 1, (DMSO-d6, 400 MHz) δ (ppm), 2.5; s, 1H, CH=N, 9; m, Ar-H, 6.7 – 8; s, 3H, O-CH_3, 3.8; s, 3H, CH_3, 1.2; s, 2H, O-CH_2, 3.89. **Figure** 3, showed the molecular weight of compound 1 is 312.39.

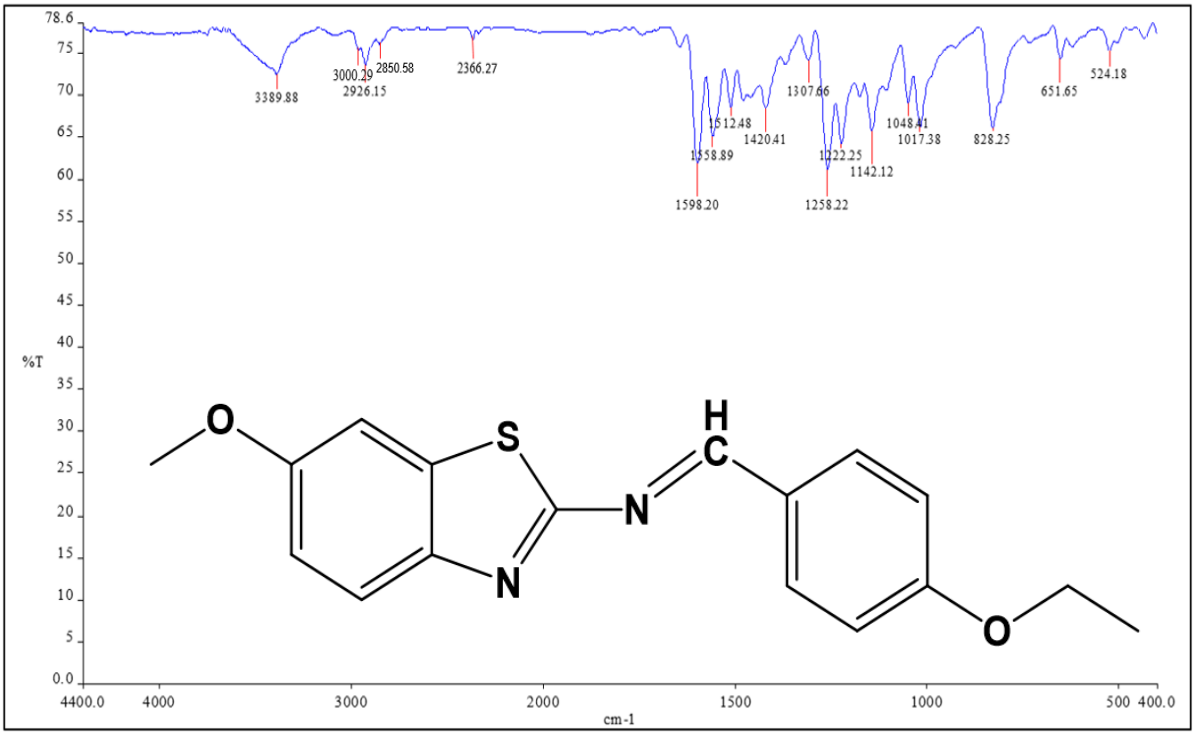


Figure 1. FT-IR analysis of compound 1

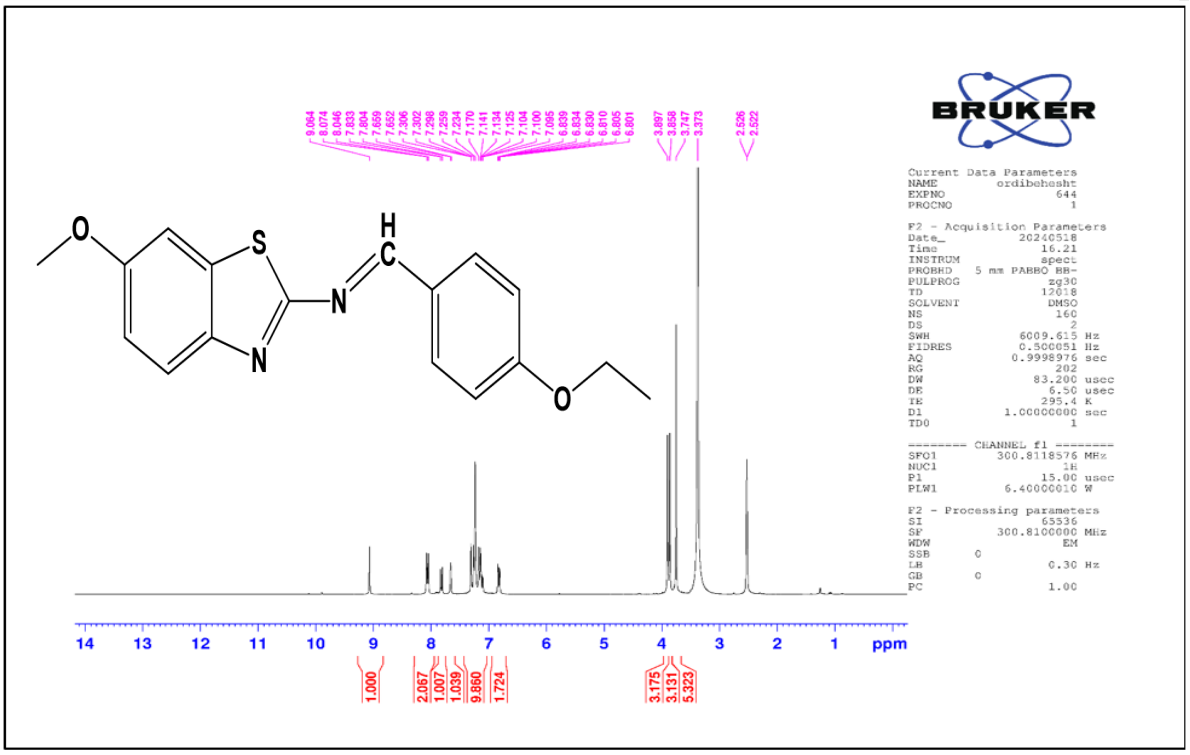


Figure 2. ^{1}H-NMR analysis for compound 1

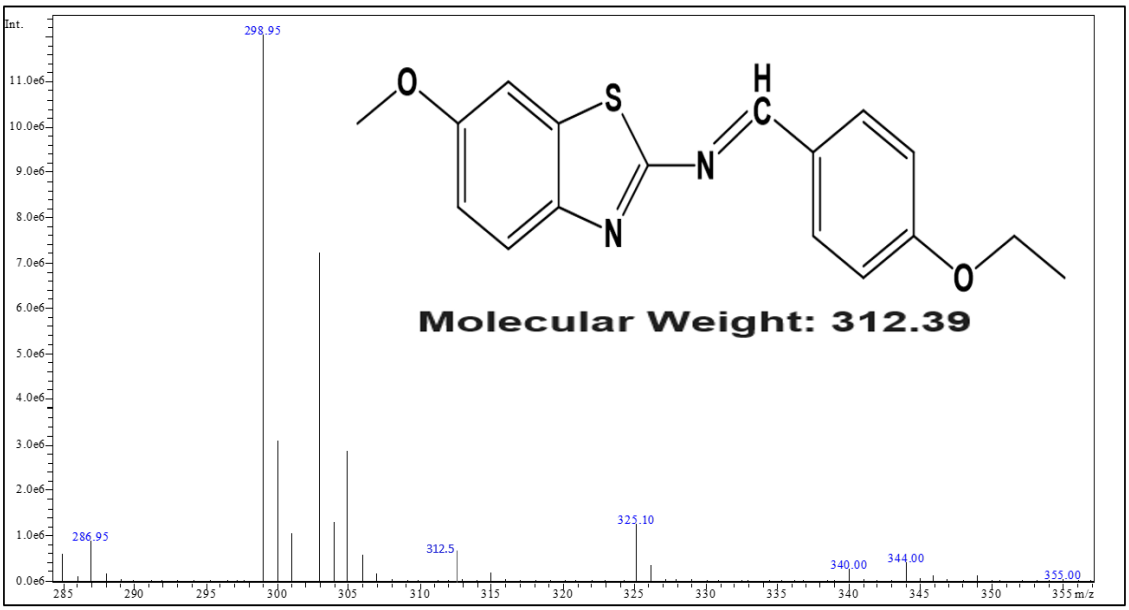


Figure 3. Mass spectrum analysis for compound 1

Figure 4, showed FT-IR bands of the compound 2 (HC=N stretching (1601.94 cm^{-1}), C-H aromatic (2924.73 cm^{-1}), S-H stretching (2362.43 cm^{-1}), N-H stretching (3387.83 cm^{-1}), O-CH_3 stretching (1462.36 cm^{-1}), O-H (3255.55 cm^{-1}) stretching, and C=C stretching (1516.08 cm^{-1}). **Figure** 5, showed ^{1}H-NMR for compound 2, (DMSO-d6, 400 MHz) δ (ppm), 2.5; s, 1H, CH=N, 9.8; m, Ar-H, 6.8 – 7.9; s, 3H, O-CH_3, 3.8; O-H, 10.9. **Figure** 6, showed the molecular weight of compound 1 is 284.33.

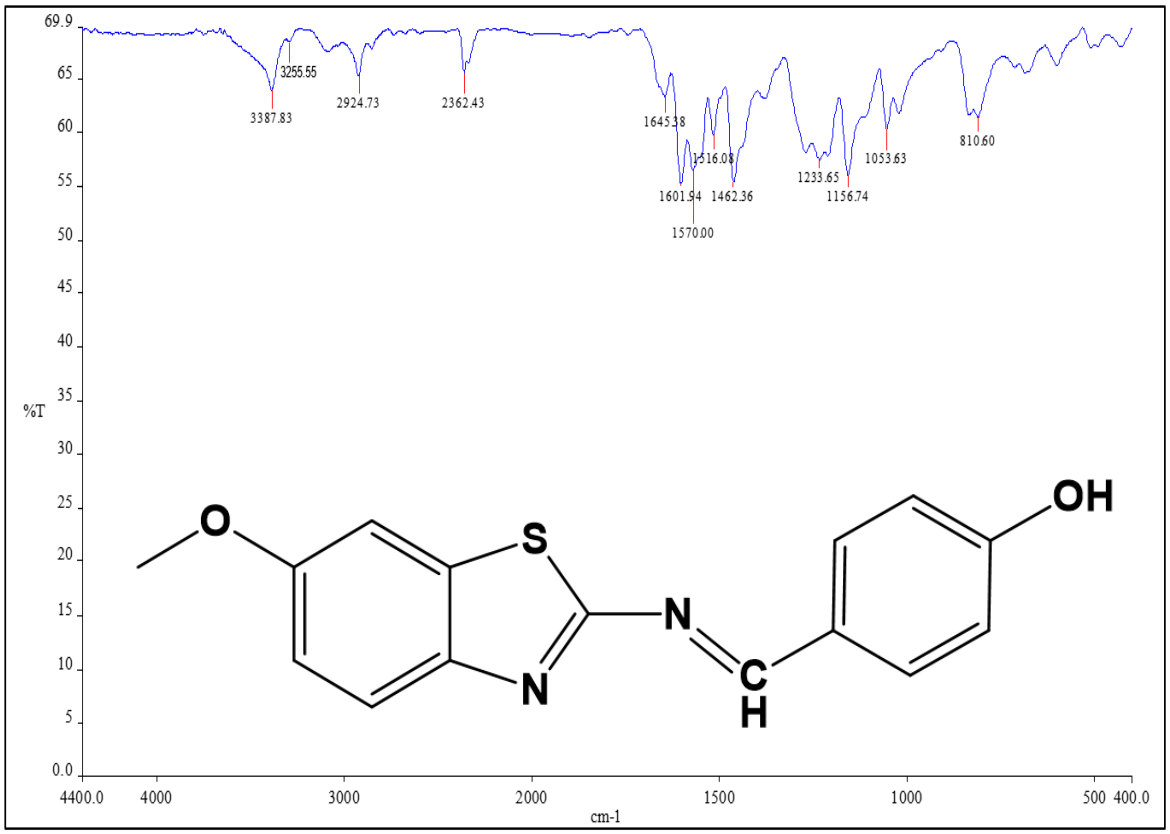


Figure 4. FT-IR analysis of compound 2.

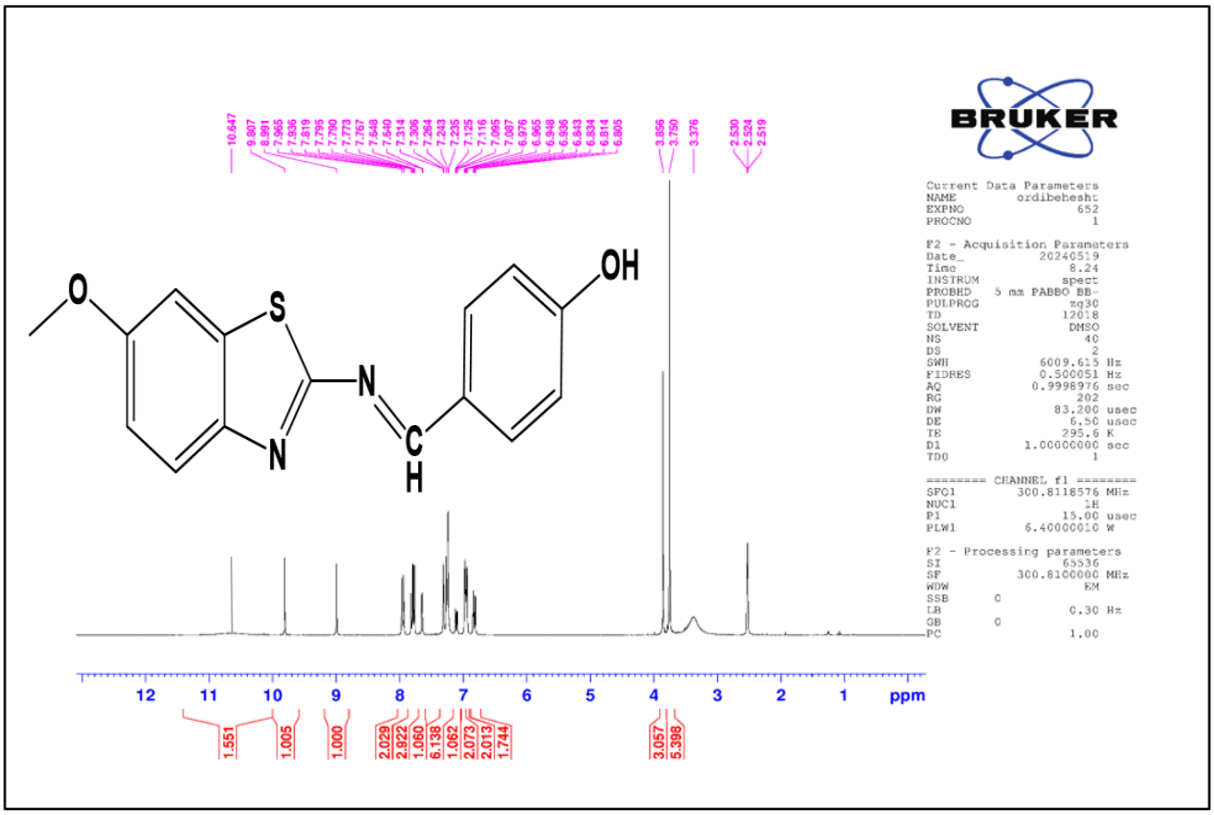


Figure 5. H-NMR analysis of compound 2.

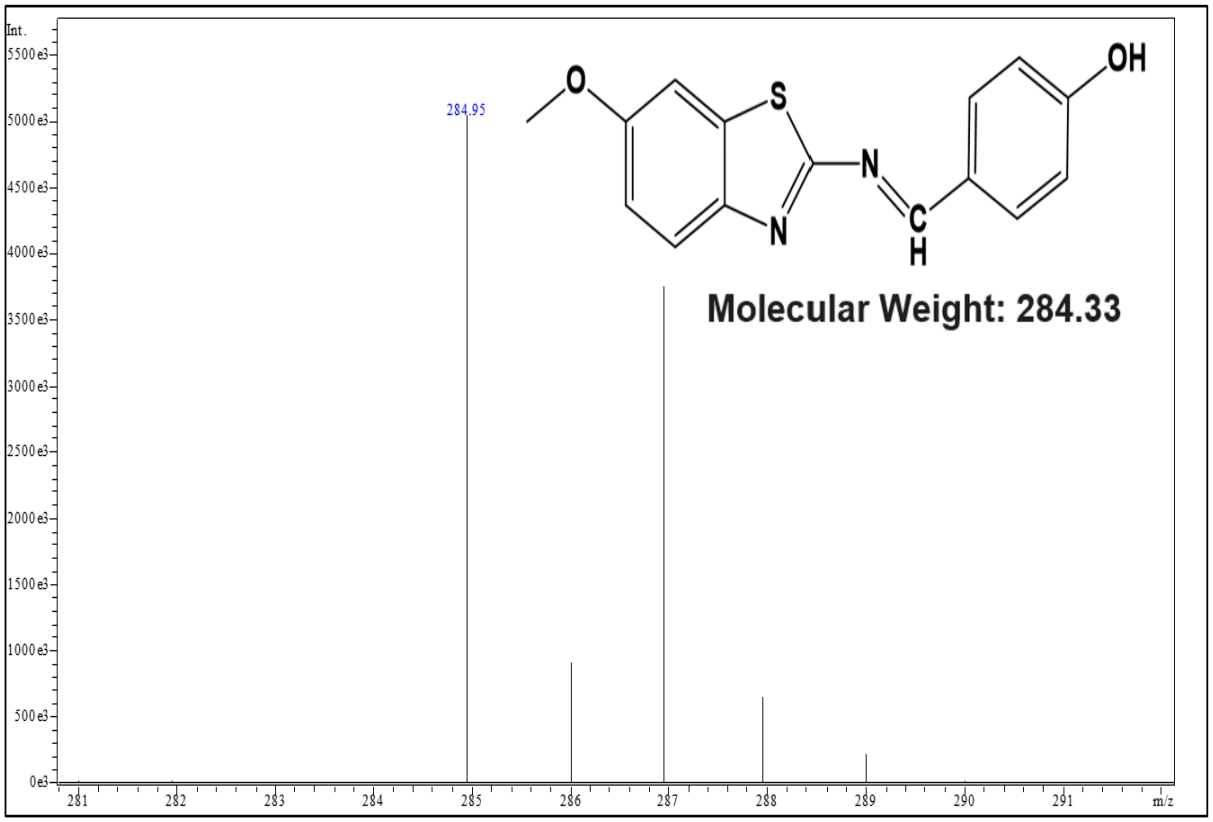


Figure 6. Mass spectrum analysis for compound 2.

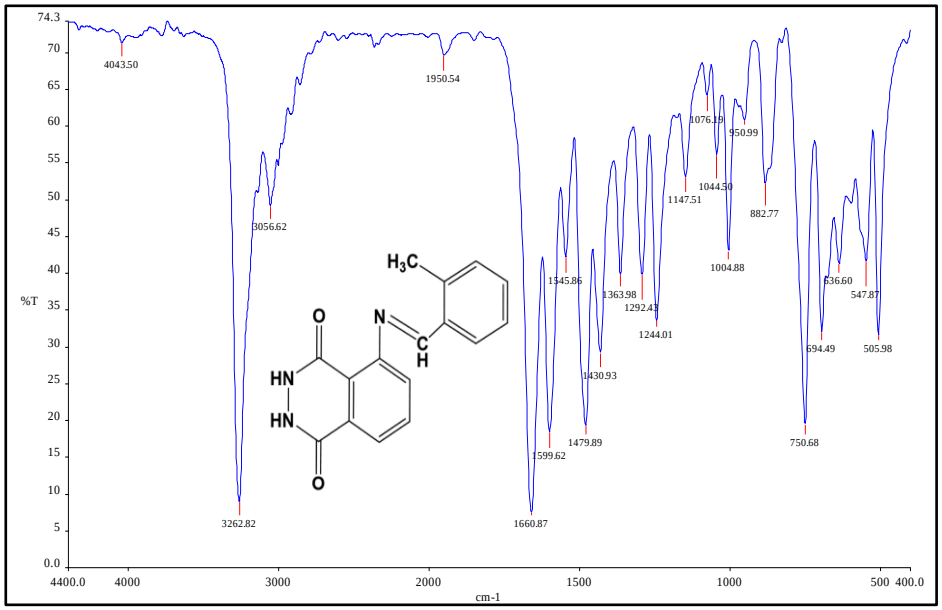


Figure 7. FT-IR analysis of compound 3

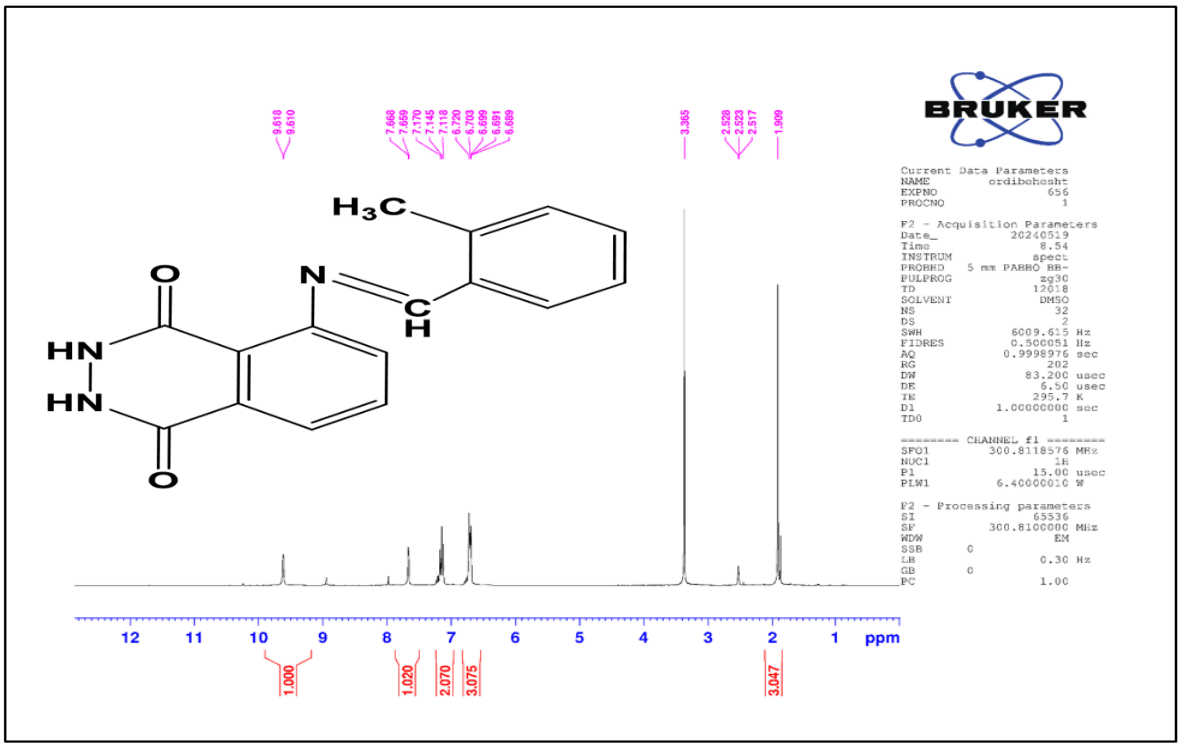


Figure 8. ^{1}H-NMR analysis for compound 3.

Figure 7, showed FT-IR bands of the compound 3 (HC=N stretching (1599.62 cm^{-1}), C-H aromatic (3056.62 cm^{-1}), C=O stretching (1660.87cm^{-1}), N-H stretching (3262.82 cm^{-1}), CH_3 stretching (1950.54 cm^{-1}), and C=C stretching (1545.86 cm^{-1}). Figure 8, showed ^{1}H-NMR analysis for compound 3 (DMSO-d6, 400 MHz) δ (ppm), 2.5; s, 1H, CH=N, 9.6; m, Ar-H, 6.1 – 7.6; s, 3H, N-H, 1.9. **Figure** 9, showed the molecular weight of compound 3 is 279.30.

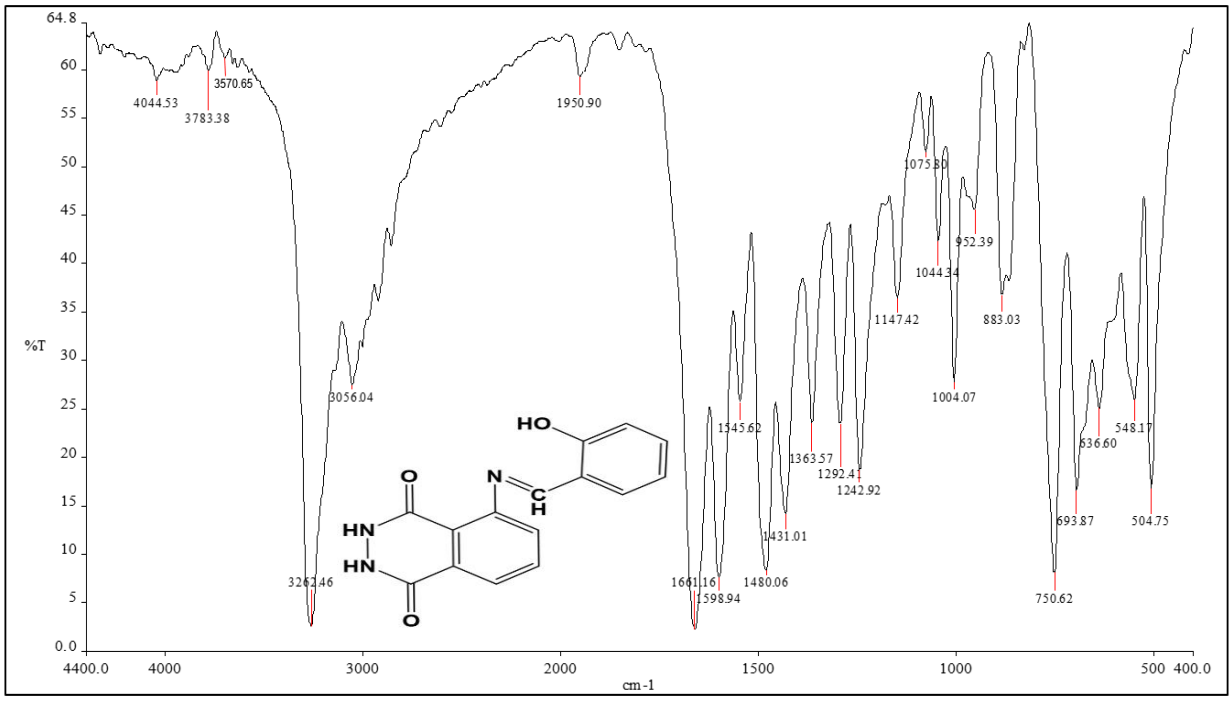


Figure 9. FT-IR analysis of compound 4.

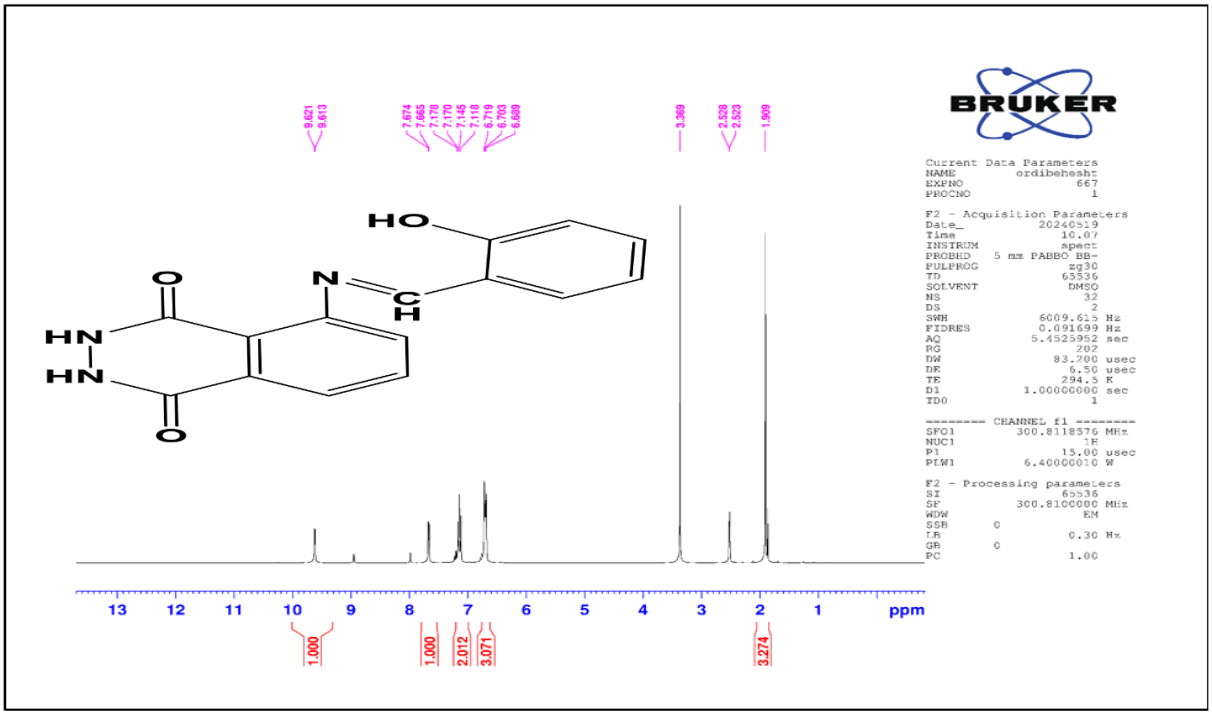


Figure 10. [1]H-NMR analysis for compound 4.

Figure 9, showed FT-IR bands of the compound 4 (HC=N stretching (1598.94 cm^{-1}), C-H aromatic (3056.04 cm^{-1}), C=O stretching (1661.16 cm^{-1}), N-H stretching (3262.46 cm^{-1}), O-H stretching (3570.65 cm^{-1}), and C=C stretching (3570.65 cm^{-1}). **Figure** 10, showed [1]H-NMR for compound 4 (DMSO-d6, 400 MHz) δ (ppm), 2.5; s, 1H, CH=N, 9; m, Ar-H, 7.1 – 7.6 ; s, 3H, N-H, 6.7; s, 1H, O-H, 9.6. **Figure** 11, showed the molecular weight of compound 4 is 281.27.

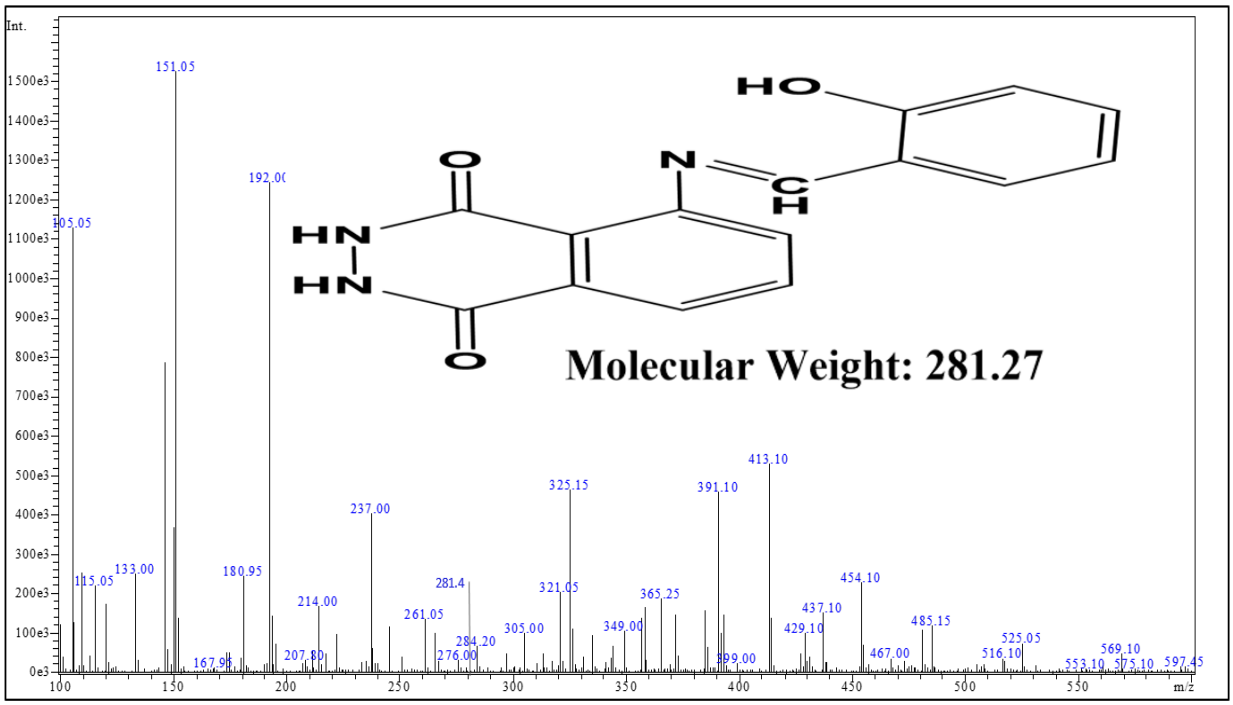


Figure 11. Mass spectrum analysis of compound 4.

To enhance the biological functions of these compounds, the anti-breast cancer activity was examined via MTT assay and estimated IC_{50} values against MDA-MB-231 cancer cells [22]. Compound 1 has IC_{50}=165.7 µg/ml, compound 2 has IC_{50}=224.9 µg/ml, compound 3 has IC_{50}=582.2 µg/ml, and compound 4 has IC_{50}=5212.9 µg/ml, as shown **Table** 1. The compound 1 has lower IC_{50} value which can be develop for further future investigations.

Table 1. Anti-breast cancer activity (IC_{50} value) for compounds (1-4).

Symbol	IC_{50} value (µg/ml)
Compound 1	165.7
Compound 2	224.9
Compound 3	582.2
Compound 4	5212.9

Table 2. MIC values of compounds against *E. coli, S. aureus,* and *C. albicans*

Symbol	*E. coli* ATCC 11775	*S. aureus* ATCC 12600	*C. albicans* ATCC 11006
Compound 1	2.5	1.25	0.625
Compound 2	2.5	1.25	0.625
Compound 3	2.5	2.5	0.0048
Compound 4	1.25	2.5	0.0097

In **Table** 2, the antibacterial activity (MIC) was examined, compounds 1 and 2 showed MIC value = 1.25 mM against *S. aureus*, compound 4 has MIC values= 1.25 mM against *E. coli*. For *C. albicans*, compound 1 and 2 = 0.625 mM, compound 3 =0.0048 mM, and compound 3=0.0048 mM, and compound 4= 0.0097 mM, **Table** 2. These results of compounds enhanced the antifungal activity against *C. albicans*. Especially compounds 3 and 4. Which means could be develop it uses and functions with merit investigation [23].

CONCLUSION

Fundamental Finding : The synthesized Schiff base compounds demonstrated notable biological activities, with compound 1 exhibiting the strongest anticancer potential, compounds 1 and 2 showing meaningful antibacterial effects, and compound 4 displaying promising antifungal activity. **Implication :** These findings highlight the chemical versatility of the synthesized derivatives and suggest that Schiff bases can serve as valuable lead structures in the development of multifunctional therapeutic agents. **Limitation:** However, the current study is limited by its reliance on preliminary biological screening without extensive mechanistic, structural–activity relationship (SAR), or in vivo validation, which restricts the generalizability of the results. **Future Research :** Further investigations should therefore include comprehensive SAR studies, computational modeling, and advanced biological evaluations—including cytotoxicity profiling, mechanistic assays, and in vivo testing—to optimize these compounds and explore new derivatives with enhanced pharmacological efficacy.

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