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Original Research Article

Activity of Quercetin Derivatives as Antibacterial, Antioxidant and Anticancer Agents

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ABSRTACT

Quercetin is a natural flavonoid known for its antioxidant, antibacterial, and anticancer activities, but its therapeutic application has been limited by its moderate potency, low bioavailability, and poor water solubility. This study aimed to synthesize derivatives of quercetin with a view to enhancing its biological activity. Three Schiff base derivatives of quercetin (W1, W2, and W3) were synthesized by condensation with selected aniline derivatives. Their structures were verified by proton nuclear magnetic resonance (^{1}H-NMR), carbon-13 nuclear magnetic resonance (^{13}C-NMR), and Fourier-transform infrared (FT-IR) spectroscopy. Antibacterial activity was determined using agar well diffusion assay with cephalexin (30 mg/mL) used as the positive control. Antioxidant activity was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay. Cytotoxicity against HepG2 hepatocellular carcinoma cells was assessed by the methyl thiazolyl tetrazolium (MTT) assay. Antibacterial activity screening revealed inhibition zones of 17 mm against *Staphylococcus aureus* and *Escherichia coli* for quercetin, compared to 17/15 mm (W1), 15/14 mm (W2), and 13/12 mm (W3), while cephalexin produced inhibition zones of 20 mm and 25 mm against *Staphylococcus aureus* and *Escherichia coli*, respectively. Quercetin , W1 showed similar antioxidant activity, each with an IC_{50} of 2.6 µg/mL, while W2 and W3 exhibited stronger antioxidant activity, with IC_{50} values of 1.8 µg/mL and 1.6 µg/mL, respectively. Quercetin and its derivatives demonstrated strong and dose-dependent reductions in HepG2 cell viability, with IC_{50} values of 185.8 µg/mL, 186.1 µg/mL, 213.7 µg/mL, and 244.3 µg/mL for quercetin, W1, W2, and W3, respectively. These results indicate that Schiff base derivatization enhances the antioxidant potential of quercetin while preserving comparable antibacterial and anticancer properties, positioning W1–W3 as potential lead compounds for future therapeutic development.

Keywords: Schiff base, Quercetin, 2,2-Diphenyl-1-picrylhydrazyl, Antibacterial, Antioxidant, Anticancer.

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Introduction

Flavonoids represent a broad collection of plant-derived polyphenolic compounds occurring abundantly in various fruits, vegetables, and medicinal plants. Flavonoids are valued for their extensive health-promoting effects.[1-3] Over the past decades, these natural compounds have been subject of biomedical research due to their strong anti-inflammatory, antioxidant, antibacterial, and anticancer properties.[4-6] Structurally, flavonoids encompass several subclasses, including flavones, flavonols, and flavanones, whose biological functions are shaped by differences in hydroxylation, glycosylation, and conjugation patterns.[7] Because of its strong anti-inflammatory, anti-cancer, anti-bacterial, and antioxidant properties, quercetin (3,3′,4′,5,7-pentahydroxyflavone) stands out among these substances as one of the most researched flavonols.[8-12] Extensive research comparing quercetin with its chemically modified derivatives has shown that structural modifications can boost antioxidant and antimicrobial activity, while retaining cytotoxic activity against cancer cells.[13-17] Despite these pharmacological benefits, quercetin is hindered by poor water solubility, low bioavailability, and rapid metabolic degradation, which collectively limit its clinical use.[11,18]

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To overcome these challenges, the development of Schiff base derivatives, which are formed by condensing quercetin's carbonyl group with primary amines has emerged as a promising strategy. Such modifications can improve quercetin's stability, aqueous solubility, and overall biological activity, while maintaining the core flavonoid structure.[19,20] These derivatives allow structural fine-tuning, which may enhance free radical scavenging and antibacterial effects, supporting their potential as bioactive agents. In this study, three Schiff base derivatives of quercetin (W1, W2, and W3) were synthesized, and thoroughly assessed for their antibacterial, anticancer, and antioxidant activities using the agar well diffusion, MTT assay, and DPPH radical scavenging assay, respectively. This comparative investigation aims to identify derivatives with superior bioactivity compared with quercetin itself, thus, laying the foundation for the development of new therapeutic candidates targeting oxidative stress, microbial infections, and hepatocellular carcinoma.

Materials and Methods

Chemicals

Quercetin (≥95% purity, HPLC grade) was supplied by Sigma Aldrich (St. Louis, MO, USA). Benzene (≥99%), concentrated hydrochloric acid (37%), and absolute ethanol (≥99.8%, HPLC grade) were products of Merck (Darmstadt, Germany). Analytical-grade aniline derivatives (≥98% purity) were purchased from Sigma Aldrich, St. Louis, Missouri, USA. Double-distilled water was used to prepared all the aqueous solution. All solvents and reagents were used as supplied without further purification.

Synthesis of Schiff base derivatives

The Schiff base derivatives of quercetin were synthesized through an acid-catalyzed condensation process involving quercetin (0.604 g) and individual aniline derivatives (1mmol each). Initially, quercetin was

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dissolved in 10 mL of absolute ethanol containing 2-3 drops of concentrated HCl, and the mixture was brought to boiling in a 150 mL glass beaker. In a separate step, each aniline derivative (1 mmol) was dissolved in 10 mL of ethanol. The two solutions were combined and exposed to microwave irradiation for 15 minutes using a NN-SM332W microwave system (Panasonic Corporation, Osaka, Japan). The progress of the reaction was monitored using thin-layer chromatography (TLC) on silica gel 60 F254 aluminum plates (Merck, Germany) employing suitable solvent systems. After the reaction was complete, the mixture was chilled in an ice bath for one hour to facilitate crystal formation.[21] The precipitated product was collected by filtration, rinsed with chilled ethanol, and recrystallized from benzene to obtain pure Schiff base derivatives. The general reaction scheme is illustrated in Figure 1, where R denotes the different aniline derivatives employed in the condensation reaction.

The synthesized compounds were characterized by different spectroscopic methods, with melting points determined using a Stuart SMP30 apparatus (Cole-Parmer, UK).

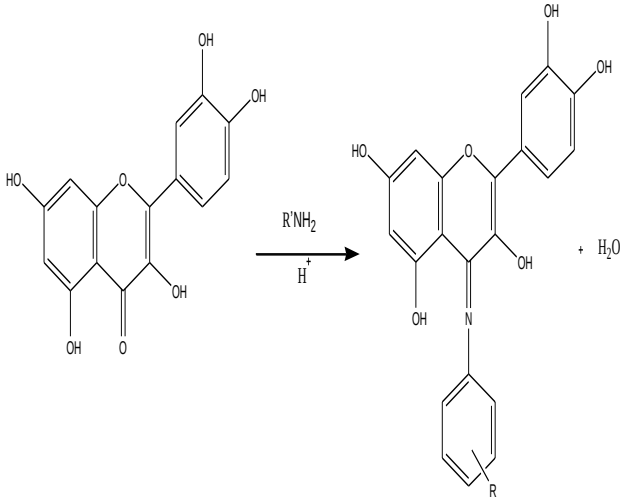

Figure 1: The general reaction scheme used for the synthesis of the Schiff base derivatives

Biological activity screening

Determination of antibacterial activity

The antibacterial activity of quercetin (Q) and its Schiff base derivatives (W1 - W3) were evaluated against *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) using the agar well diffusion method as previously described.[22,23] Cephalexin (30 mg/mL) was used as the positive control, while dimethyl sulfoxide (DMSO) served as the negative control. The bacterial suspensions used to seed Mueller–Hinton Agar (MHA; Oxoid, UK) plates were standardized to 10^8 CFU/mL. Circular wells (7 mm in diameter) were bored into the agar, and 50 µL of each compound (100 mg/mL in dimethyl sulfoxide [DMSO]) was added to the wells. After incubation for 24 hours at 36 ± 1°C, the inhibition zones were measured in millimeters.

Determination of antioxidant activity

The antioxidant activity of quercetin and its Schiff base derivatives (W1 – W3) was determined using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging assay, following the method reported by Brand-Williams *et al*. (1995).[24] Serial dilutions of each sample (7.8 – 1000 µg/mL) were prepared in methanol and mixed with 100 µL of 0.2 mM DPPH solution in a 96-well microplate. The mixtures were incubated in the dark at room temperature for 30 minutes, after which the absorbance was measured at 515 nm using a Wave XS2 microplate reader (BioTek Instruments, Vermont, USA). Determination was done in duplicate, and ascorbic acid was used as the positive control.

Determination of anticancer activity

The cytotoxic effect of quercetin and its Schiff base derivatives against HepG2 human hepatocellular carcinoma cells was assessed using the MTT assay, following the procedure described by Mosmann (1983).[25] Cells were maintained in RPMI-1640 medium (Gibco, Thermo Fisher Scientific, USA) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. For the experiment, 1×10^4 cells per well were seeded in 96-well plates and treated with graded concentrations of each compound (7.4 – 600 µg/mL) for 24 hours. After exposure, MTT solution (0.5 mg/mL) was introduced to each well, followed by a 4-hour incubation period to facilitate the formation of formazan crystals. These crystals were solubilized in 100 µL of dimethyl sulfoxide (DMSO), and absorbance was measured at 570 nm using the same microplate reader. The experiment was performed in duplicate. IC_{50} values, indicative of the concentration that reduces cell viability by 50%, were derived from nonlinear regression analysis of dose-response data.

Statistical analysis

All data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software, version 26.

Results and Discussion

Physicochemical properties of the synthesized compounds

The synthesized compounds were identified as follows:

W1:2-(3,4-dihydroxyphenyl)-4-((3-hydroxyphenyl)imino)-4*H*-chromene-3,5,7-triol; light yellow crystals, molecular weight 393.35 g/mol, melting point 160 - 162°C, yield 57.90%.
W2:4-((4-bromophenyl)imino)-2-(3,4-dihydroxyphenyl)-4*H*-chromene-3,5,7-triol; orange crystals, molecular weight 456.25 g/mol, melting point 178 - 179°C, yield 65.27%.
W3:2-(3,4-dihydroxyphenyl)-4-(p-tolylimino)-4*H*-chromene-3,5,7-triol; green crystals, molecular weight 391.38 g/mol, melting point 183 - 185°C, yield 55.20%.

The chemical structures of the compounds are shown in Table 1, while their mass spectral data (ESI-MS), obtained using a Bruker micrOTOF-Q II instrument (Bruker Daltonics, Germany), are illustrated in Figures 2 – 4.

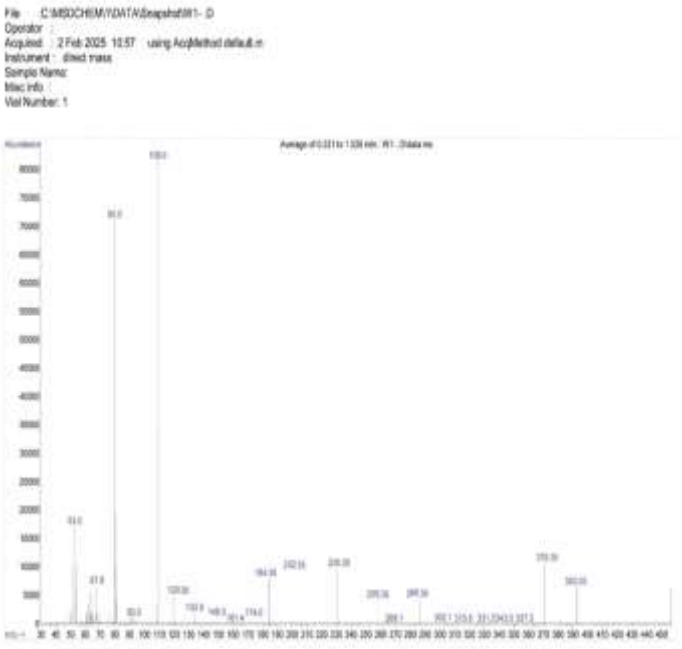

Figure 2: Mass spectrum of compound W1

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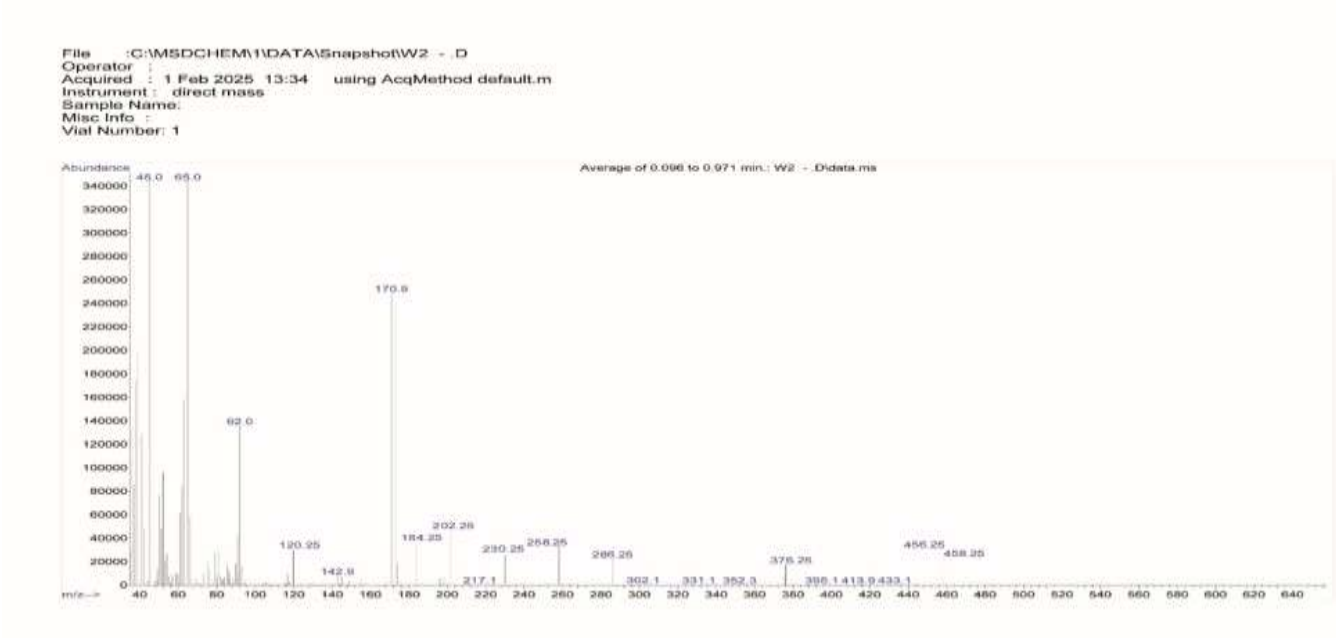

Figure 3: Mass spectrum of compound W2

Figure 4: Mass spectrum of compound W3

Spectroscopic characterization of compounds W1 – W3

The structures of the synthesized Schiff base derivatives (W1 - W3) were confirmed through FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectral analysis. In the FTIR spectra, for all derivatives, the characteristic carbonyl (C=O) stretching vibration of quercetin was absent, replaced by a distinct imine (C=N) band at 1659, 1658, and 1655 cm^{-1} for W1, W2, and W3, respectively (Figures 5 - 7; Table 2). This spectral change is a well-established marker of Schiff base formation and is in agreement with previous findings for flavonoid-derived imines.[26] Additional functional group features were observed in each compound. W1 exhibited a broad O-H stretch band at 3281 cm^{-1}, W2 displayed a characteristic C–Br absorption at 592 cm^{-1}, and W3 showed a weak aliphatic C–H stretch at 2956 cm^{-1}, corresponding to a p-tolyl methyl group. Such structural modifications to the flavonoid framework can influence solubility and biological activity, as the Schiff base linkage alters the electronic distribution around the quercetin nucleus, potentially enhancing its bioactive properties.[27] The ^{1}H-NMR spectra (Figure 8 - 10; Table 3) confirmed the formation of Schiff base linkages, as evidenced by CH=N proton signals at δ 8.52, 8.50, and 8.48 ppm for W1, W2, and W3, respectively, alongside the retention of hydroxyl protons. The most deshielded hydroxyl proton (OH-3) consistently appeared at δ 12.50 ppm, indicative of strong intramolecular hydrogen bonding, a feature often associated with enhanced antioxidant activity.[28] Aromatic proton resonances are observed in the δ 6.8 - 7.8 ppm range, characteristic of the flavonoid skeleton. In addition, W3 displayed a singlet at δ 2.51 ppm, confirming the presence of a methyl substituent on the aromatic ring.

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Table 1: Codes and chemical structures of the quercetin derivatives

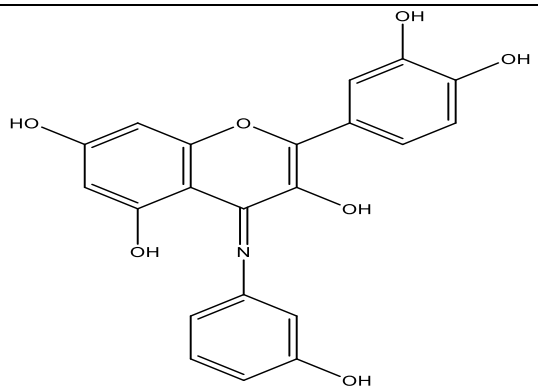
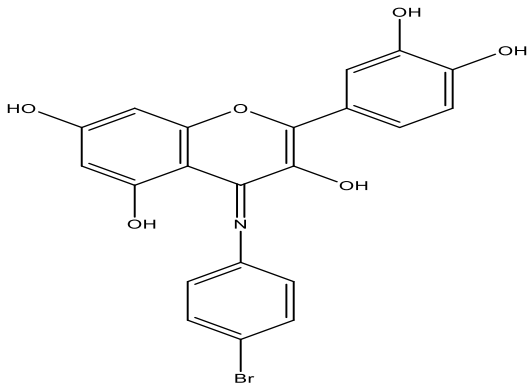
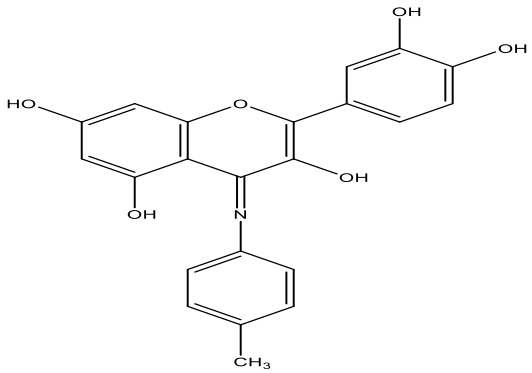
Code	Chemical Structure
W1	
W2	
W3	

Table 2: FT-IR spectral data and assignments of compounds W1, W2, and W3

Compound	Vibration frequency (cm^{-1})					
	C=N	**C=C**	**O-H**	**C-Br**	**C-H (Aliphatic)**	**C-H (Aromatic)**
W1	1659 (m)	1606 (s)	3281 (m) & 1354 (m)	-	-	3100 (w)
W2	1658 (m)	1606 (s)	3269 (m)	592 (m)	-	3050 (w)
W3	1655 (m)	1605 (m)	3259 (m)	-	2956 (w)	3050 (w)

(s) = strong, (m) = medium, (w) = weak

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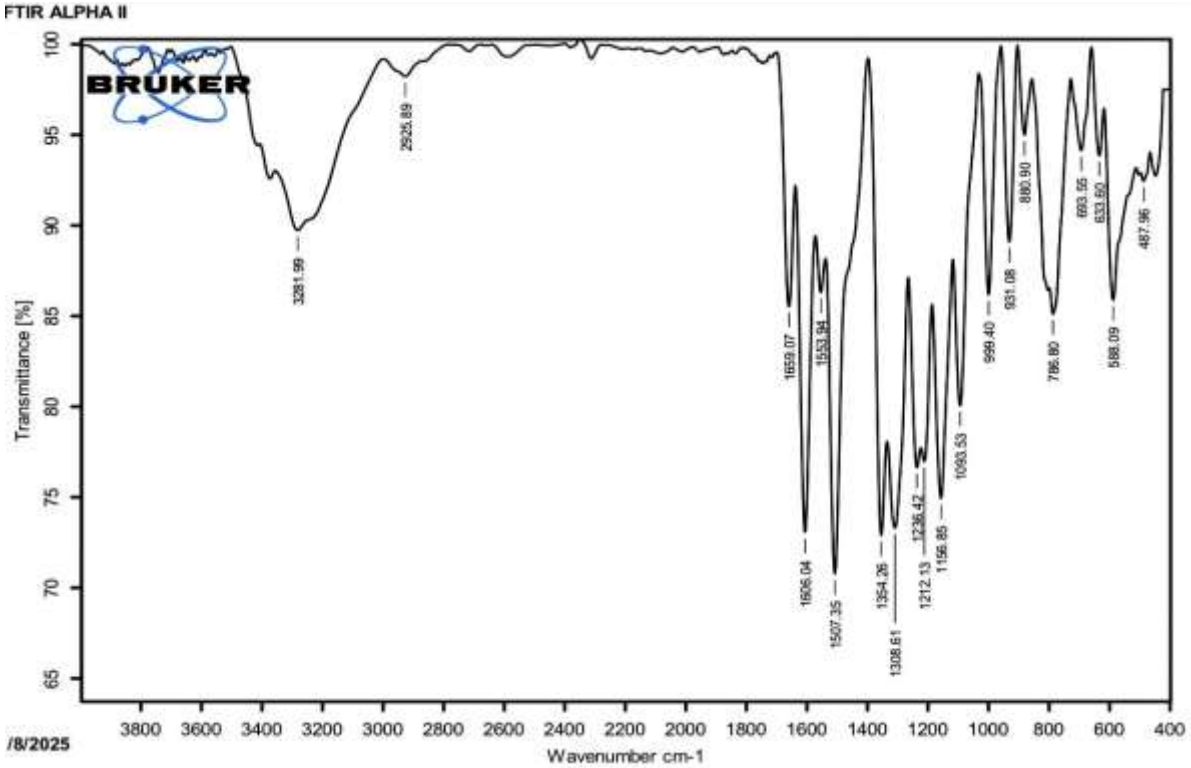

Figure 5: FT-IR spectrum of compound W1

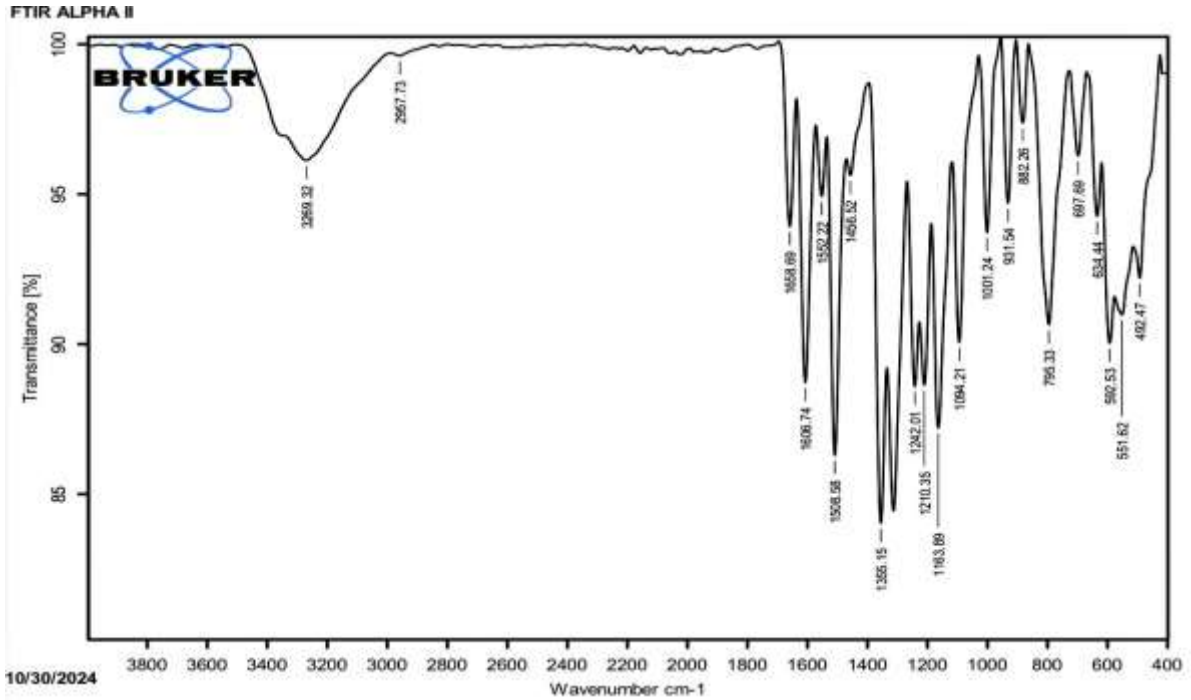

Figure 6: FT-IR spectrum of compound W2

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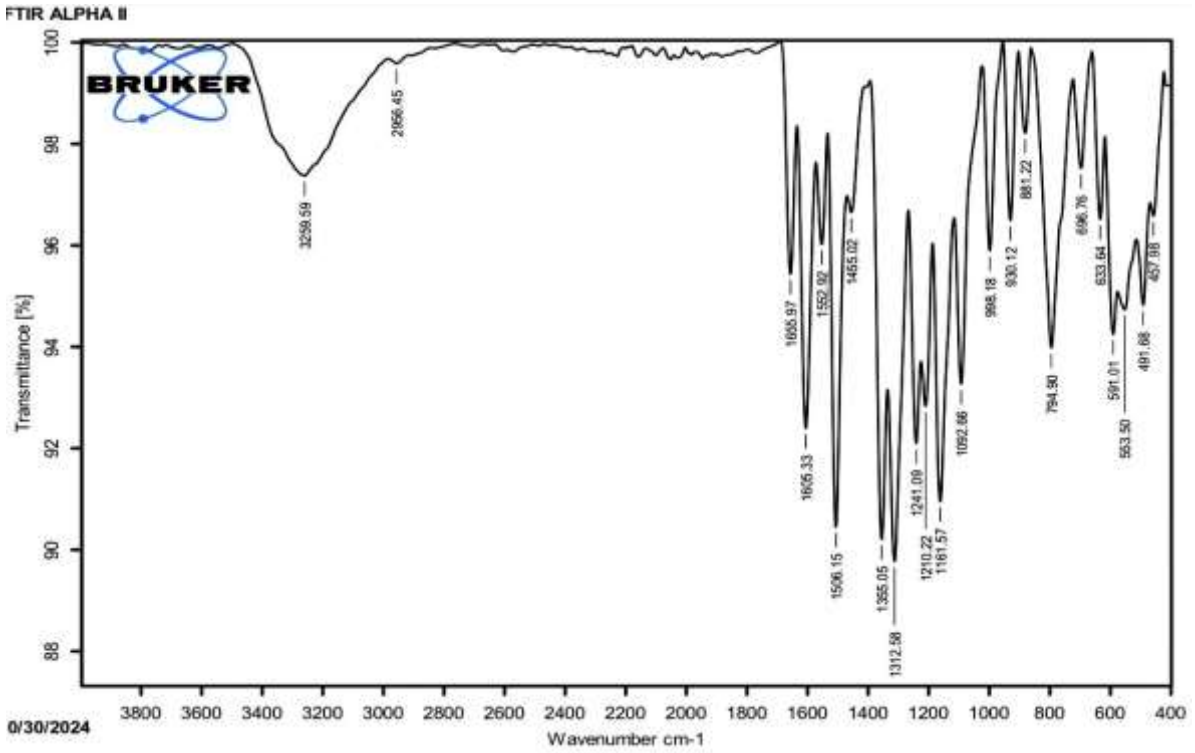

Figure 7: FT-IR spectrum of compound W3

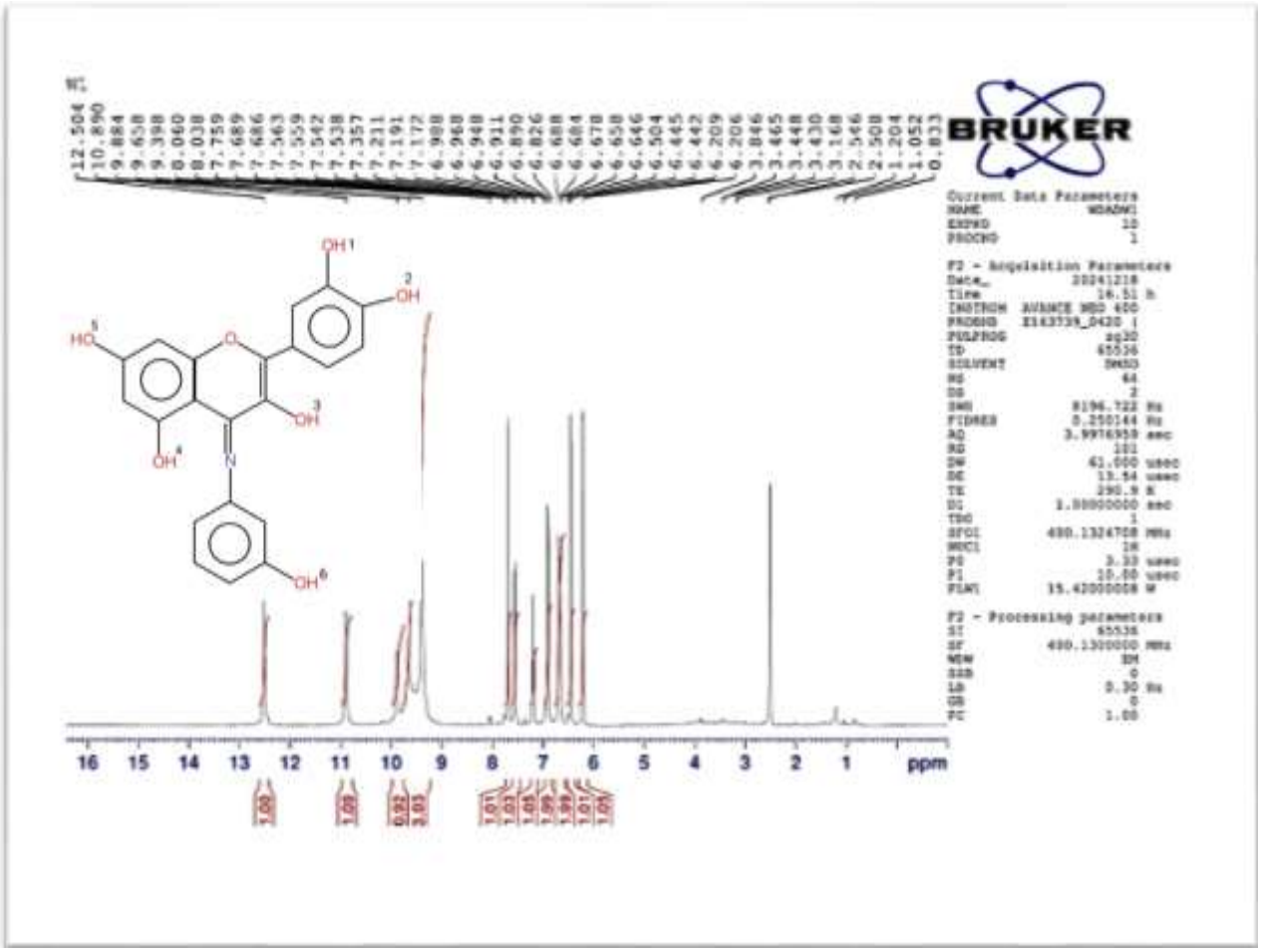

Figure 8: [1]H-NMR spectrum of compound W1

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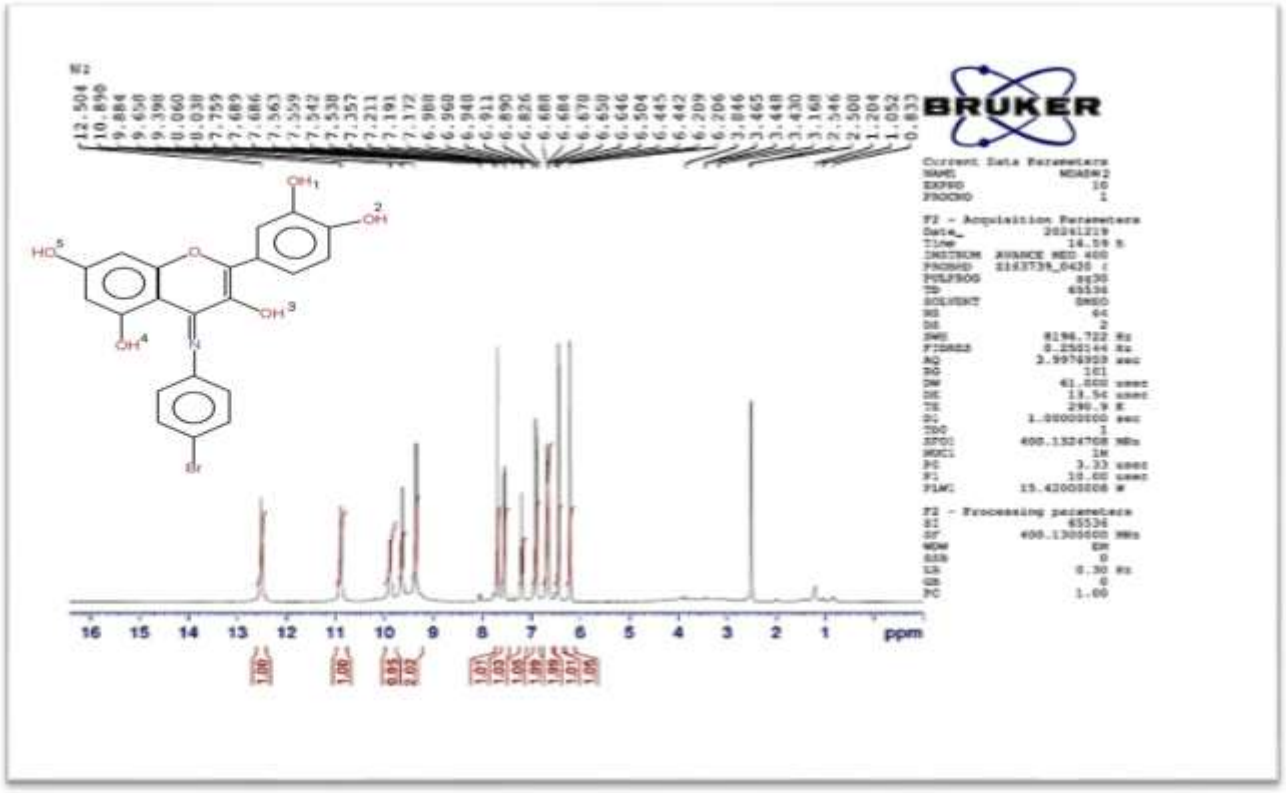

Figure 9: ¹H-NMR spectrum of compound W2

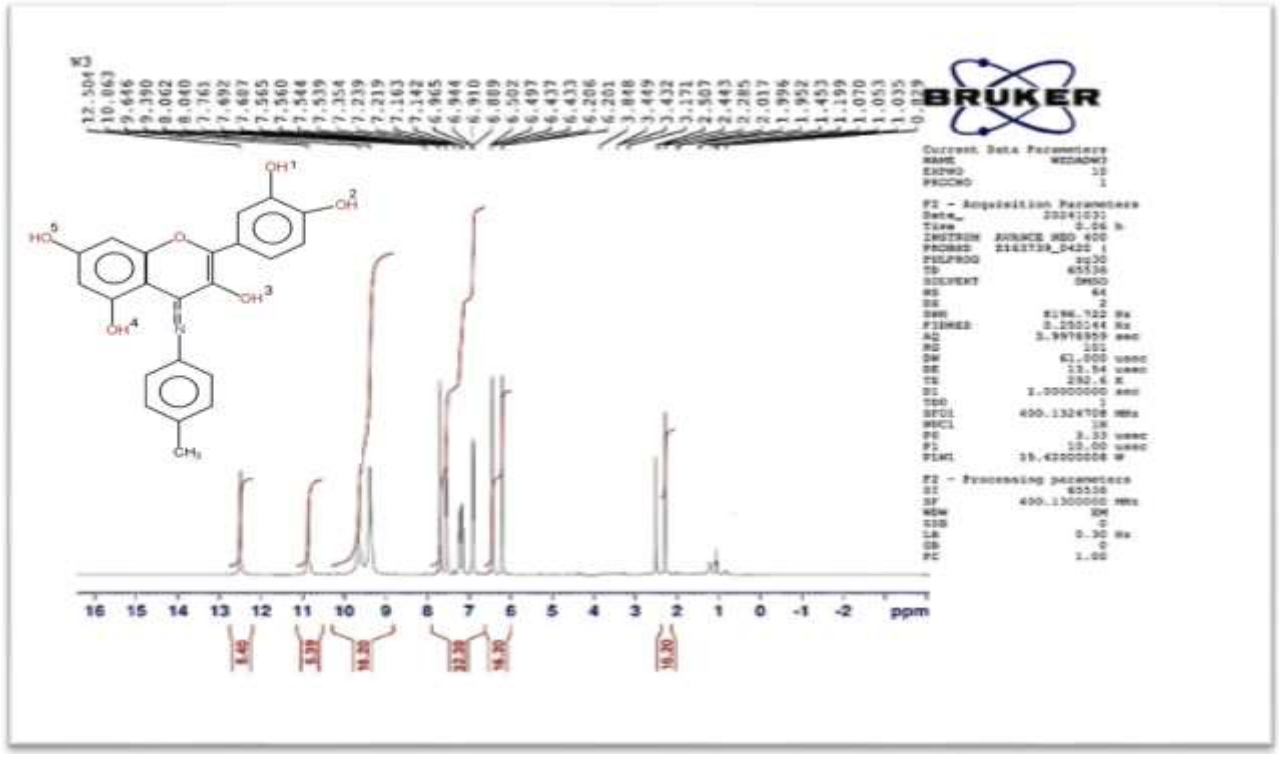

Figure 10: ¹H-NMR spectrum of compound W3

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Table 3: ^{1}H-NMR spectral data of compounds W1, W2, and W3

Compound	Chemical shifts (δ, ppm) in in DMSO-d_6						
	CH=N	**OH-3**	**OH-4**	**OH-5**	**OH-1, OH-2, OH-6**	**Aromatic protons**	**CH_3 (Methyl protons)**
W1	8.52 (s, 1H)	12.50 (s, 1H)	10.89 (s, 1H)	9.88 (s, 1H)	9.40-9.88 (m)	6.90-7.80 (m)	-
W2	8.50 (s, 1H)	12.50 (s, 1H)	10.89 (s,1H)	9.88 (s, 1H)	9.40-9.88 (m)	6.88-7.76 (m)	-
W3	8.48 (s, 1H)	12.50 (s, 1H)	10.86 (s, 1H)	9.65 (s, 1H)	9.39-9.65 (m)	6.92-7.78 (m)	2,51 (s, 3H)

The ^{13}C-NMR spectra (Figure 11 - 13; Table 4) further substantiated the structural assignments, showing the disappearance of the carbonyl carbon resonance (~176 ppm) and the emergence of a new imine carbon signal around δ 148 ppm. Aromatic carbons resonated within their expected ranges (C1–C4: δ 113–147 ppm; C5–C7: δ 115–156 ppm). A notable upfield shift of C16 in W3 (δ 148 ppm), relative to W1 and W2 (δ 156 ppm), was observed, reflecting the electron-donating influence of the methyl group. Such an effect can enhance π-electron delocalization, potentially improving the radical scavenging properties of the compound.[29] These combined spectroscopic data confirmed the successful synthesis of the Schiff base derivatives and reveal structural variations that may contribute to modulating their bioactivity, aligning with findings reported for other quercetin-based analogues.[30,31]

Table 4: ^{13}C-NMR spectra data of compounds W1, W2, and W3

Carbon Number	Chemical shifts (δ, ppm) in in DMSO-d_6		
	W1	**W2**	**W3**
C=N	147–148	147–148	148
C=O (Absent)	—	—	—
C1, C4	113–116	113–116	113–116
C2, C3	145–147	145–147	145–147
C5, C6	115–122	115–122	115–122
C7	154–156	154–156	154–156
C10, C12, C14	93–130	—	—
C11	164	164	161
C13	161	161	164
C16	156	156	148
C17	112.57	116	120
C18	158.77	~135	130
C19	112.57	120	136
C20	130	~135	130
C21	109	116	120
C22 (CH_3)	—	—	20

Antibacterial activity of quercetin and its derivatives

Quercetin produced potent antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, with inhibition zone diameters of 17 mm for both bacterial strains. Compound W1 exhibited comparable antibacterial activity as the parent compound (quercetin), with inhibition zone diameter of 17 mm and 15 mm against *Staphylococcus aureus* and *Escherichia coli*, respectively. W2 showed slightly reduced antibacterial activity, producing zones of inhibition of 15 mm and 14 mm against *Staphylococcus aureus* and *Escherichia coli*, respectively, whereas W3 exhibited moderate activity with inhibition zone diameters of 13 mm and 12 mm against *Staphylococcus aureus* and *Escherichia coli*, respectively (Table 5). Cephalexin, as expected, demonstrated the most pronounced activity, with inhibition zone diameters of 20 mm and 25 mm against *Staphylococcus aureus* and *Escherichia coli*, respectively validating the reliability of the assay. These findings suggest that Schiff base modification of the flavonoid scaffold can maintain or even modulate antibacterial properties, potentially through improved solubility and enhanced interactions with bacterial cell membranes.[32]

Table 5: Antibacterial activity of quercetin and its Shiff base derivatives (W1, W2, and W3)

Compound	Inhibition zone diameter (mm)	
	***Staphylococcus* aureus**	***Escherichia coli***
Quercetin	17	17
W1	17	15
W2	15	14
W3	13	12
Standard (Cephalexin, 30 mg/mL)	20	25
Control (DMSO)	0	0

Antioxidant activity of quercetin and its derivatives

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Quercetin and its Schiff base derivatives exhibited progressively higher DPPH radical scavenging effects as their concentrations increased. Native quercetin displayed scavenging capacities ranging from 53.6% to 94.6%, corresponding to an IC_{50} of 2.61 µg/mL. Compound W1 exhibited a comparable trend, with scavenging activity between 58.1% and 91.8% and an IC_{50} value of 2.60 µg/mL. Notably, derivatives W2 and W3 demonstrated superior antioxidant activity, achieving lower IC_{50} values of 1.8 µg/mL and 1.6 µg/mL, respectively (Table 6). The enhanced radical scavenging capacity observed for W2 and W3 may be attributed to the electron-donating and radical-stabilizing effects of bromine and methyl substituents, a phenomenon consistent with previous reports on chemically modified flavonoids.[33-35]

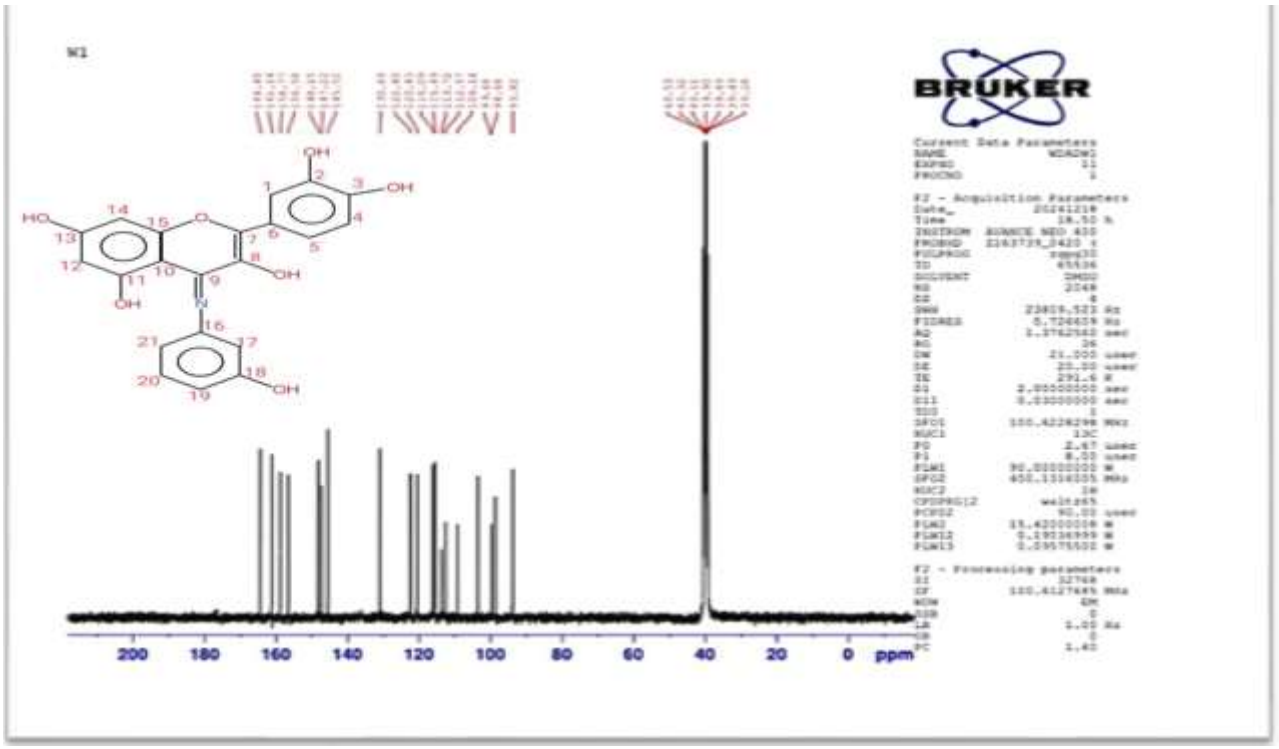

Figure 11: ^{13}C-NMR spectrum of compound W1

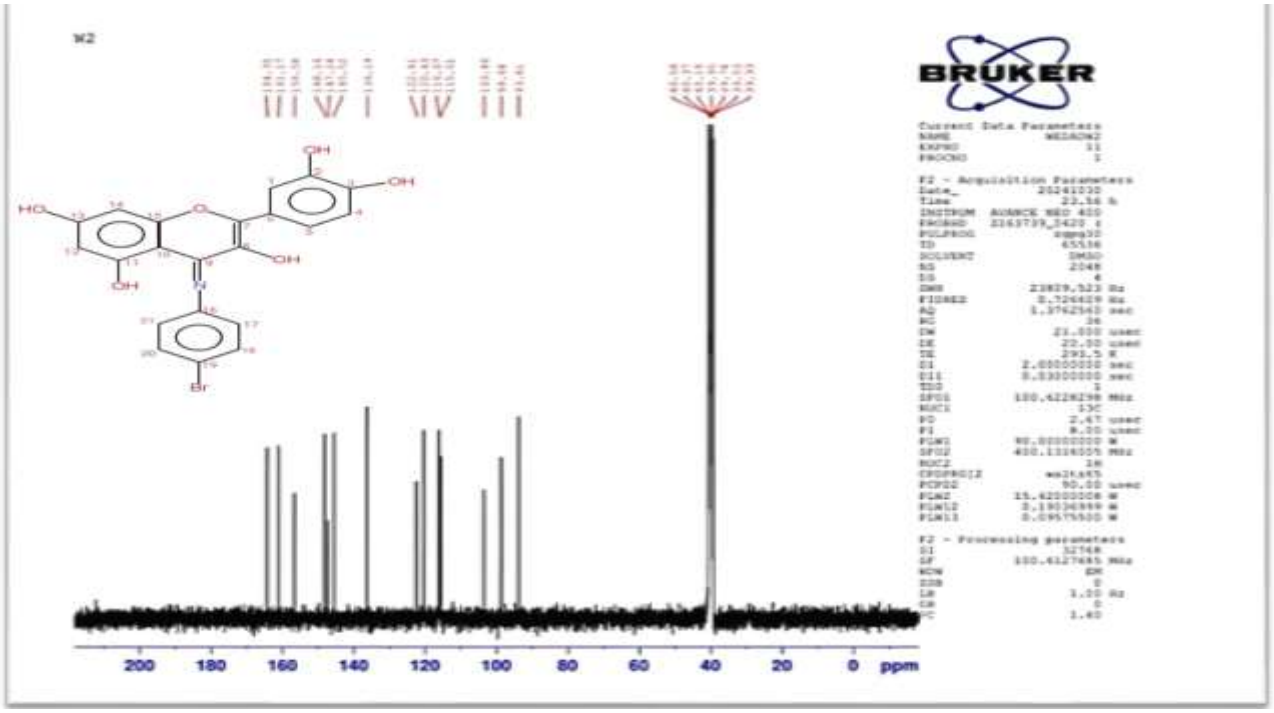

Figure 12: ^{13}C-NMR spectrum of compound W2

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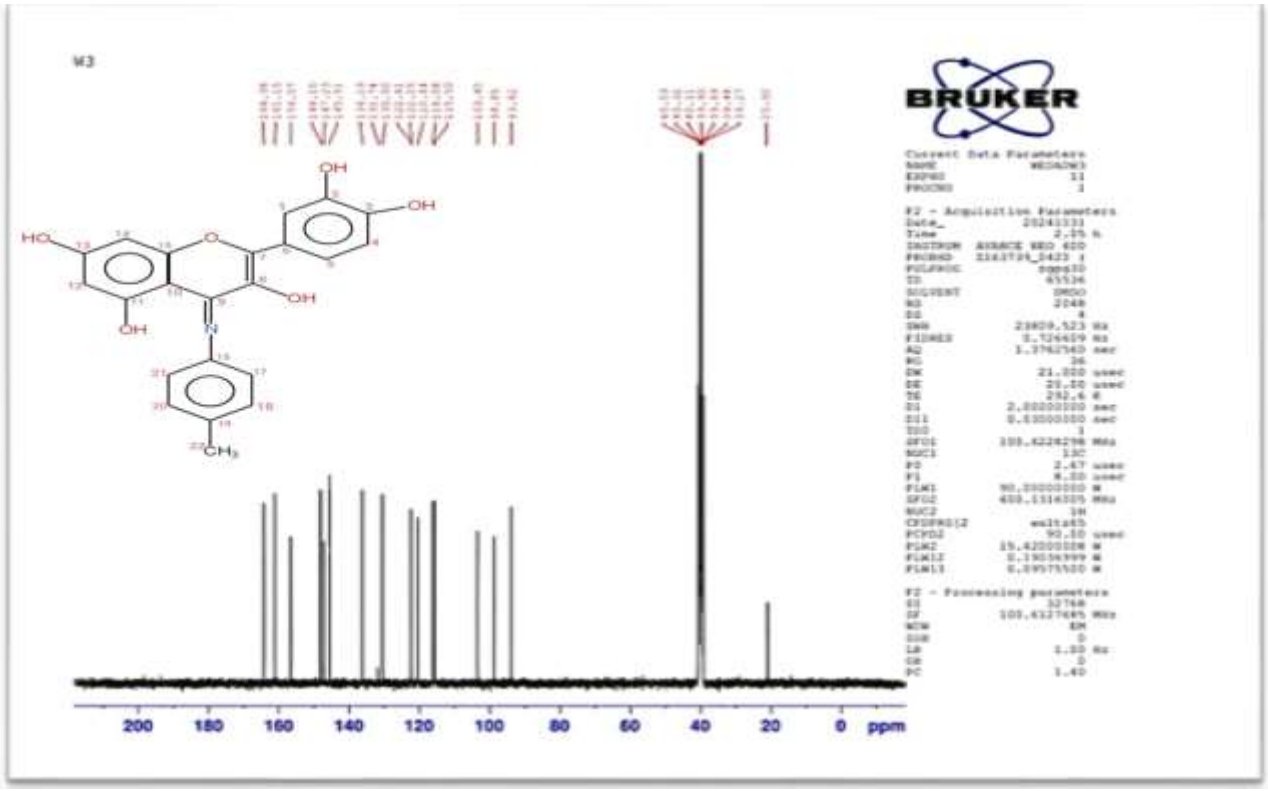

Figure 13: ^{13}C-NMR spectrum of compound W3

Table 6: Antioxidant activity of quercetin and its Shiff base derivatives (W1, W2, and W3)

Compound	DPPH radical scavenging activity (%) at different concentration								
	IC_{50}	1000 µg/mL	500 µg/mL	250 µg/mL	125 µg/mL	62.5 µg/mL	31.2 µg/mL	15.6 µg/mL	7.8 µg/mL
Quercetin	2.6	94.6 ± 0.5	94.0 ± 0.8	89.9 ± 0.7	85.6 ± 1.0	84.4 ± 0.0	74.4 ± 0.3	62.2 ± 0.0	53.6 ± 3.8
W1	2.6	91.8 ± 0.2	91.4 ± 0.1	90.8 ± 0.6	80.9 ± 0.5	72.3 ± 0.2	67.9 ± 0.2	64.7 ± 0.2	58.1 ± 0.2
W2	1.8	91.5 ± 0.2	90.4 ± 0.2	89.8 ± 0.4	88.2 ± 0.2	77.1 ± 0.7	70.1 ± 0.5	67.8 ± 0.3	56.3 ± 0.6
W3	1.6	87.2 ± 0.2	85.1 ± 0.1	83.4 ± 0.6	81.3 ± 0.2	79.5 ± 0.7	72.4 ± 0.1	69.5 ± 0.5	49.3 ± 1.1

Cytotoxicity activity of quercetin and its derivatives

All compounds demonstrated dose-dependent reductions in cell viability across the tested concentrations (7.4 - 600 µg/mL) (Table 7). Quercetin decreased cell viability from 87.85% at 7.4 µg/mL to 36.05% at 600 µg/mL, with an IC_{50} of 185.77 µg/mL, which is in line with its documented pro-apoptotic activity.[32,34] W1 and W2 displayed comparable cytotoxic profiles, reducing HepG2 cell viability from 95.87 to 41.28% and from 94.23 to 42.86%, respectively, with IC_{50} values of 186.06 µg/mL and 213.74 µg/mL, respectively. These findings suggest that Schiff base modification maintains the intrinsic cytotoxicity of quercetin, potentially aided by enhanced lipophilicity and improved membrane permeability.[36] W3 exhibited comparatively weaker effects, decreasing cell viability from 96.43 to 45.36%, with an IC_{50} of 244.34 µg/mL. This reduced potency may be attributed to diminished cellular uptake associated with the methyl substituent. Nevertheless, all derivatives demonstrated potent anticancer activity, with W1 and W2 having similar efficacy as that of the parent compound.

Table 7: Cytotoxicity activity of quercetin and its Shiff base derivatives (W1, W2, and W3) against HepG2 cells

Compound	HepG2 cell viability (%) at varying concentrations					
	IC_{50}	600 µg/mL	200 µg/mL	66.66 µg/mL	22.22 µg/mL	7.4 µg/mL
Quercetin	185.77	36.05 ± 0.92	44.21 ±0.92	67.13 ± 1.50	79.61 ± 1.61	87.85 ± 3.11
W1	186.06	41.28 ± 1.23	49.29 ± 0.87	56.22 ± 1.73	66.43 ± 1.44	95.87 ± 2.81
W2	213.74	42.86 ± 0.14	46.58 ± 2.38	60.20 ± 1.15	76.63 ± 0.14	94.23 ± 8.44
W3	244.34	45.36 ± 0.07	52.50 ± 4.55	58.62 ± 2.38	64.54 ± 3.25	96.43 ± 0.29

Conclusion

In this study, three Schiff base derivatives of quercetin (W1, W2, and W3) were successfully synthesized, and their structures were confirmed through FT-IR, ^{1}H-NMR, and ^{13}C-NMR analyses, collectively verifying the presence of imine bonds and the anticipated structural modifications. Biological investigations revealed that these derivatives preserved or enhanced the bioactivities of native quercetin, particularly in terms of antioxidant and antibacterial effects. Among the derivatives, W3 exhibited the most potent antioxidant capacity, whereas W1 demonstrated antibacterial and cytotoxic profiles comparable to that of the parent compound. These findings underscore the potential of structural derivatization as a viable strategy to optimizing the pharmacological activities of quercetin. Consequently, such derivatives may represent promising leads for the development of novel antioxidant and anticancer agents, either as therapeutic candidates or as functional constituents in nutraceutical applications. Future research, including *in vivo* validation, mechanistic studies, and formulation optimization, is essential to facilitate their translation into clinical use.

Conflict of interest

The authors declare no conflict of interest

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them

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