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Article

Design and Synthesis of Heterocyclic Compounds Containing a Benzothiazole Nucleus and Study of Their Effectiveness as Antioxidants and Their Biological Applications

Wissam, M. R. Al-Joboury*[1]

1. Department of Medical Laboratory Techniques, Al-Haeija Technical Institute, Northern Technical University
* Correspondence: wassammoh911@gmail.com

Abstract: The compounds (W2) (6-(5-fluorothiophen-2-yl)-4-(quinolin-6-yl)pyrimidin-2(1H)-one) in this paper were previously made from α, β unsaturated carbonyl compounds known as chalcones. These compounds are typically made by reacting 6-quinolinearboxaldyde with 1-(5-fluorothiophen-2-yl)ethan-1-one. Following their preparation and purification, appropriate measurements of their physical, chemical, and spectroscopic characteristics were undertaken in order to get chalcones that interacted with urea under established chemical circumstances to produce the necessary pyrimidinone molecule (W2). Using glacial acetic acid as a catalyst in 100% ethanol, pyrimidine compounds interacted with substituted 2-aminobenzothazol compounds to produce novel Schiff's bases (w6–8). IR, 1H-NMR, and certain physical data were used to determine the structures of the synthesized compounds. The disk diffusion assay technique was used to investigate the antibacterial activity in vitro against Gram-positive and gram negative microorganisms. When compared to standard medications, the minimum inhibitory concentration (MIC) of thiazolidine derivatives was shown to be superior to the growth of both gram-positive and gram-negative bacteria. The DPPH technique was used to assess the antioxidant activity of produced compounds using a reference medication. The study's findings showed that, among the compounds evaluated for antioxidant activity, W6 and W8 showed promising antioxidant activity with IC50 values of 3.2μM and 27.30μM, respectively, whereas ascorbic acid, the reference component, had a value of 29.2μM. Compared to conventional ascorbic acid, compounds (W6 and W7) showed remarkable DPPH radical scavenging activity, according to the antioxidant screening results. These findings could potentially offer some important direction for the creation of novel antioxidants.

Keywords: Antioxidant, pyrimidine, Schiff bases, Biological Evaluation, 2-aminobenzothazol.

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1. Introduction

Heterocyclic compounds are among the most important classes in organic and medicinal chemistry due to their structural diversity and wide range of biological activities. Among these compounds, the benzothiazole nucleus stands out as a bicyclic aromatic system containing sulfur and nitrogen atoms, which confers distinctive electronic properties and a high capacity for interaction with biological systems. Derivatives of this nucleus have garnered increasing attention in recent years due to their potential applications in various medical and pharmaceutical fields, including as antioxidants, antimicrobials, and antitumor agents [1,2].

Interest in studying these compounds stems particularly from the critical role that free radicals play in the development of many chronic diseases, as an imbalance between the production of these radicals and the body's ability to eliminate them leads to what is known as oxidative stress. This oxidative stress is a major factor in the development of diseases such as cancer, heart disease, and neurological disorders. Hence, the need arose to develop effective compounds capable of inhibiting or scavenging these radicals, which has led researchers to explore heterocyclic systems, particularly benzothiazoles, due to their ability to scavenge free radicals thanks to their conjugated nature and their possession of electron-donating and electron-accepting atoms [3,4].

This study focuses on the design and synthesis of new compounds containing a benzothiazole core fused with other heterocyclic rings, such as thiophene and quinoline, with the aim of enhancing biological activity and improving the physical and chemical properties of these compounds. This approach is based on the principle that the incorporation of more than one ring system into a single molecule can lead to a synergistic effect that increases the compound's efficiency in reacting with free radicals or oxidants [5,6].

2. Materials and Methods

Material

All the chemicals used in this experiment were purchased from BDH Companies and Fluka. 2.2 .Tools Utilized Melting points were measured with an uncorrected measuring instrument (Automatic melting point: SMP40). Iodine was used to improve the spots in sheet polygram silica gel as the stationary phase in thin layer chromatography (TLC). Using the KBr disk, infrared spectra on a scale of 400-4000 cm^{-1} were produced using the Fourier-Transform Infrared Spectrophotometer FT-IR-600. A Bruker 500 MHz MS5973 Agilent Technology was used to study the nuclear magnetic resonance (1H, 13C-NMR) spectra of substances produced at Sannati Sharif University in Iran. DMSO-d6 was used as a solvent.

Synthesis of chalcones (w1) [7]

A solution of 10% sodium hydroxide (5 mL) and 3 mL of ethanol has been mixed with the suitable acetophenone (0.01 mol) and aromatic benzaldehyde (0.01 mol). The mixture was refrigerated for twelve hours after being agitated for two to three hours at a temperature of twenty to forty degrees Celsius. After that, it was filtered, cleaned with cold water, dried, and recrystallized from ethanol after being diluted with 30 milliliters of ice-cold distilled water. The produced chemical (w1) has a yield of 78%, is white, and has M.P. (78) C^0.

Synthesis of Pyrimidine-2(1H)-one (w2) [8]:

Chalcones (w1) had been dissolved in 0.01 mole of EtOH abs. After dissolving 0.01 mole of urea in 20 milliliters of EtONa, this was added, and the mixture was refluxed for 12 hours. After the concentrated solvent was added to ice-cold water while being constantly stirred, it was neutralized with acid, filtered, and cleaned with water. The produced chemical (w2) has a yield of 68%, is brown in color, and has M.P. (283-285) C^0.

Synthesis of substituted 2-aminobenzothazol (W3-5) [9]

Glacial was added drupe-wise to a solution of 0.1 mole of substituted aniline and 0.4 mole of potassium thiocyanate in 150 m1 of 98% acetic acid while stirring 16 g of dissolved bromine in 50 ml of glacial acetic acid at a temperature below 10 C^0. The mixture was agitated for ten hours after all of the bromine solutions were added. Warm water is used to dissolve the mixed filters. 10% Na OH was used to neutralize the combined filtrate. After being gathered on a filter and dried, the precipitate was recrystallized using an appropriate solvent. The produced compound (w1) has the following physical characteristics: it is white, M.P. (183-185) ^oC, and has a 76% yield.

Synthesis of Schiff's Bases (w6-8) [10]:

(0.01) mole of substituted 2-aminobenzothazol molecule in abs was combined with (0.01) mole of pyrimidine compounds (w2). For four hours, 25 milliliters of EtOH were mixed with a few drops of glacial acetic acid. The physical characteristics are included in Table (3,4).

An Assessment of Biological Activity

This study used two types of pathogenic bacteria: Gram-positive bacteria (Acinetobacter et al. Golden) and Gram-negative bacteria (Escherichia et al.). These bacteria were obtained from the bacteriology laboratory of the Department of Medical Laboratory Technology at Al-Hawija Technical College and were cultured on Mueller-Hinton agar medium [11]. Chemical solutions for (w-3, w-4, w-5, w-6, w-7 and w-8) were prepared at concentrations of 0.01, 0.001 and 0.0001 mg/ml using dimethyl sulfoxide (DMSO) as a solvent. In this process, the minimum inhibitory concentration (MIC) was calculated. Mueller-Hinton agar was used as the growth medium for the sensitivity testing of the bacterial isolates used in the study [12]. After preparation, the medium was sterilized, poured into plates, and allowed to solidify. Four small holes were then punched into each plate. The plates were subsequently placed in an incubator for the entire day at 37°C. The results were read the day after the experiment, revealing that the biological activity of the derivatives used depended on the diameter of the visible inhibition zone in the plates around the holes. As the diameter increased, the biological activity of the substance increased, compared to the inhibition diameter of the antibiotics [13]

Antioxidant activity [14]

Organic compounds' capacity to donate electrons or hydrogen atoms to the DPPH radical in order to form stable diamagnetic scaffolds is linked to their antioxidant activity. The potential of synthetic compounds to scavenge free radicals is demonstrated by their interaction with the stable DPPH free radical. Antioxidant-induced decrease in DPPH radical absorbance at 517 nm was utilized to gauge the radicals' capacity to be reduced. At concentrations of l mg/mL, the majority of the investigated chemicals in these series demonstrated excellent interaction with the DPPH radical. Table 5 shows the % inhibition of each synthetic compound's ability to scavenge the DPPH radical. When compared to the normal ascorbic acid, the synthesized compounds' DPPH radical scavenging activity shown exceptional results. The DPPH technique was also used to test synthetic substances for antioxidants. With IC50 values of 26.50 μM and 27.30 μM, respectively, W6 and W7 demonstrated high antioxidant activity among the compounds examined; ascorbic acid had an IC50 value of 29.2 μM. Good efficacy and derivatization of the parent molecule have produced good antioxidant efficacy, according to antioxidant studies [17, 19]. The DPPH test was used to screen the produced analogs for antioxidant activity. Samples W6 and W7 at various concentrations had their % inhibition calculated.

3. Results and Discussions

The DPPH technique was then used to assess the produced compounds' antioxidant properties. Because ascorbic acid (vitamin C) comprises hydroxyl groups and is known to be an antioxidant, it was employed as a standard in this procedure. Due to the impact of light on free radicals and the possibility of reading errors and repetition, the preparation procedure is done in the dark. Understanding the expression of IC50 is crucial. The chemical is more active in biological aspects when the value is lower, and vice versa [15-20]. The inhibitory capability of the examined drugs was investigated using a range of concentrations. Table 4 indicates that compounds W6 and W7 have the strongest antioxidant activity.

Table 1. Elemental analysis and physical characteristics of produced compounds [W3-W5].

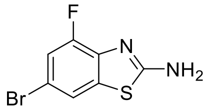
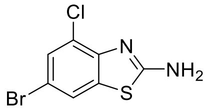
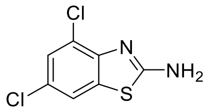
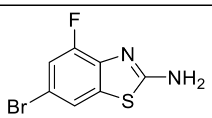
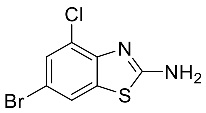
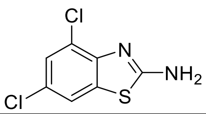
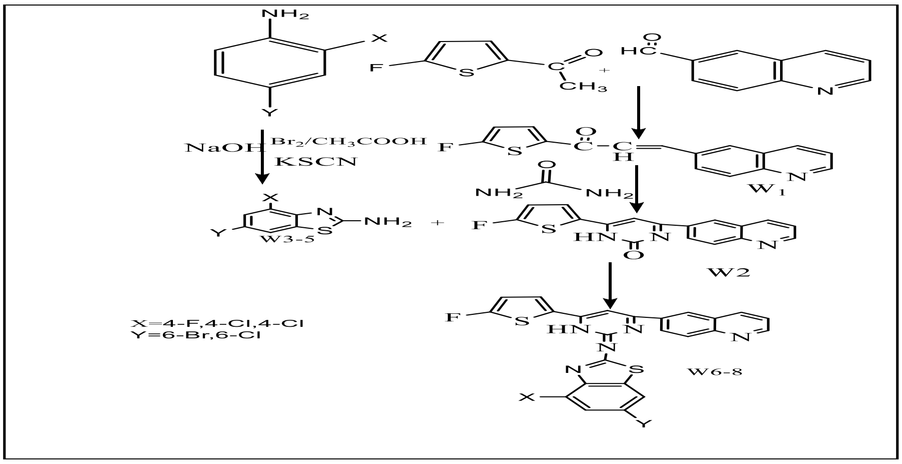
Comp. No.	substituted 2-amino benzothiazoles	Color	M.P (C^0)	T. Ref. (hr.)	Yield (%)
W_3		Yellow	218--220	24	68
W_4		Light green	232-235	24	72
W_5		with	192-194	24	83

Table 2. The produced compounds' physical characteristics [W6-W8].

Comp. No.	Color	M.P (C^0)	T. Ref. (hr.)	Yield (%)	R.f. MeOH
W_6	Dark Yellow	213	6	72	0.61
W_7	Dark Brown	194	6	64	0.66
W_8	Brawn	252	6	67	0.54

Table 3. The synthesized compounds' FT-IR data [W3-W5].

Comp. No.	R	IR (KBr) cm^{-1}					
Characterization of substituted 2-amino benzothiazoles [W_1-W_3]		**ν (NH_2)**	**ν(C-H) Arom.**	**ν (C-S-C)**	**ν (C=C)**	**ν (N=C)**	**Other**
W_3		3450-3411	3092-3028	620	1506	1696	ν(C-F) *asy.,sym.* 1234
W_4		3274-3236	3058	759	1480	1658	ν(C- Br) *asy.,sym.* 1151
W_5		3367-3354	3023	682	1444	1624	ν(C-Cl) *asy.,sym* 1172
Characterization of Schiff base [W_4-W_6]		**ν (C=N)schiff**	**ν(C-H) Arom.**	**ν (C-S-C)**	**ν (C=C)**	**ν (N=C)**	**Others**
W_3		1630	3062	1796	3417	1282	ν(C-H) *asy.,sym.* 2973,2831
W_4		1642	3061	1783	3521	1267	ν(C-H) *asy.,sym.* 2941, 2842
W_5		1687	3043	1828	3448	1230	ν(C-H) *asy.,sym.* 2913, 2810



Scheme (1) illustrates the prepared compounds (W1-11)

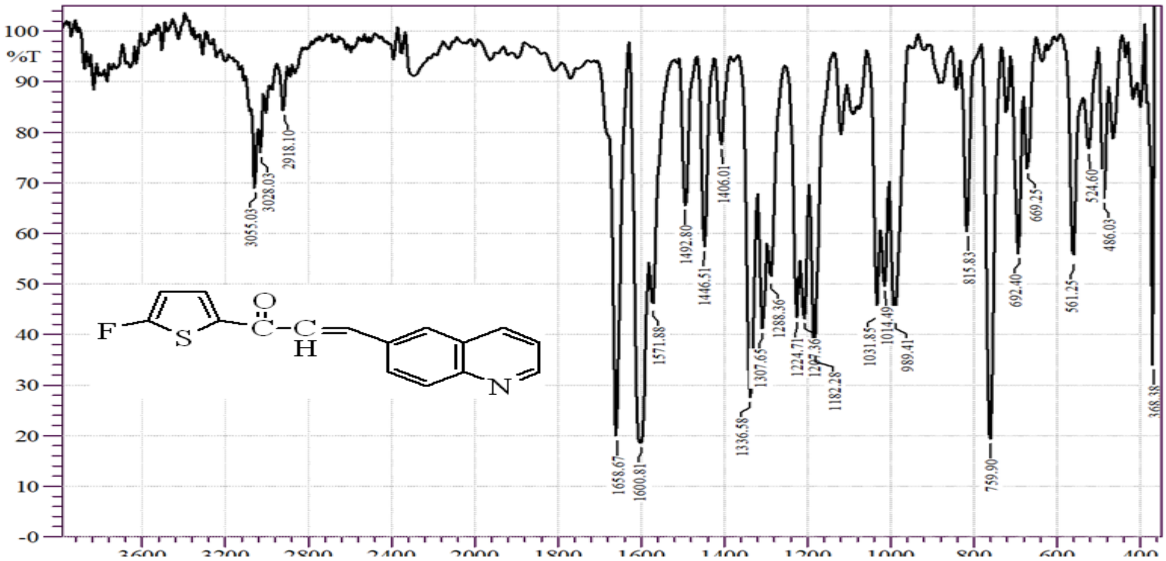


Fig.1 FT-IR of W1

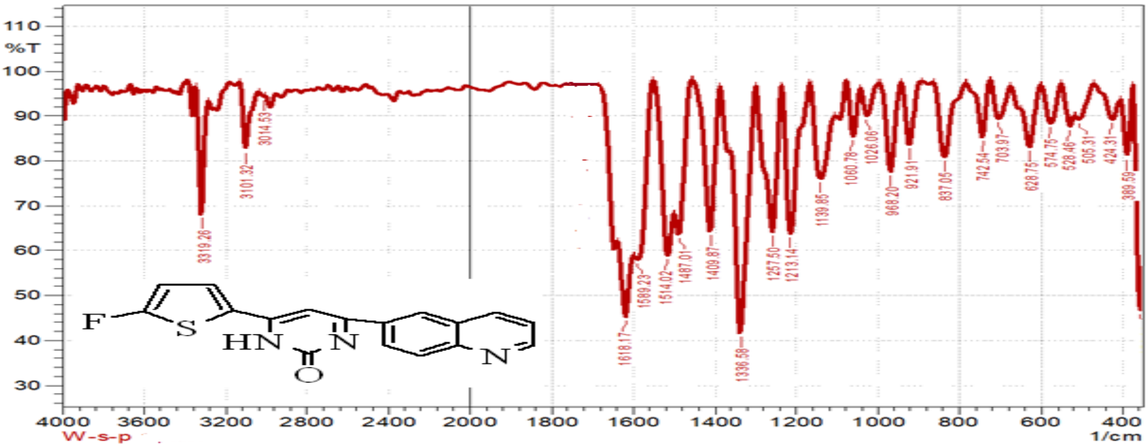


Fig.2 FT-IR of W2

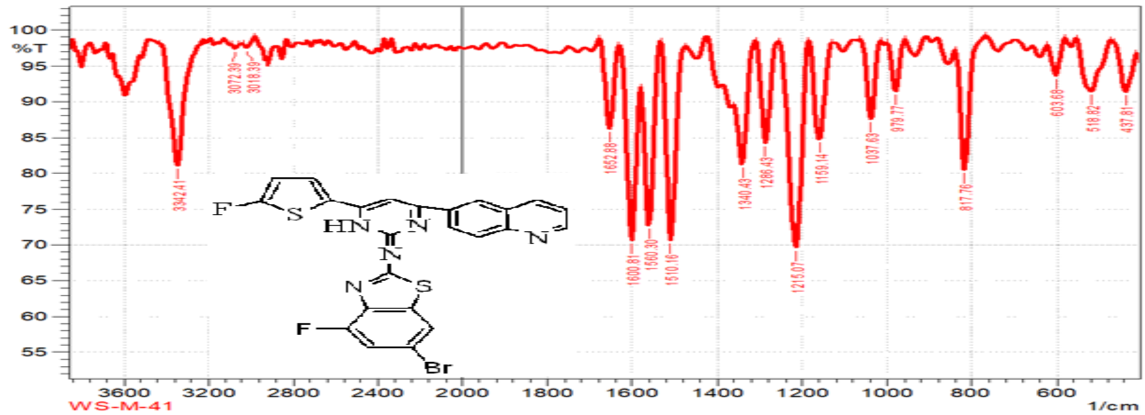


Fig.3 FT-IR of W6

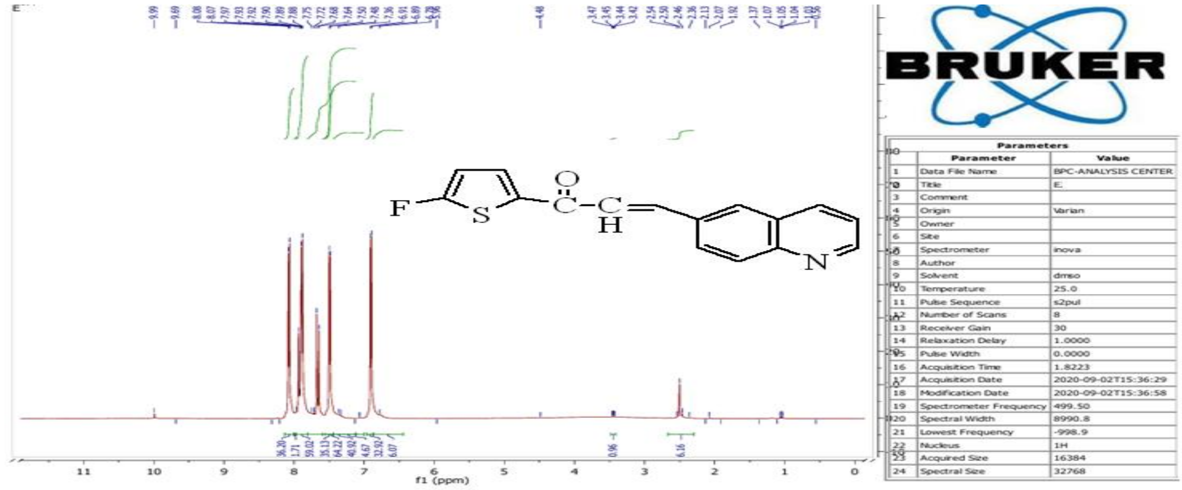


Fig.4 1H-NMR of W1

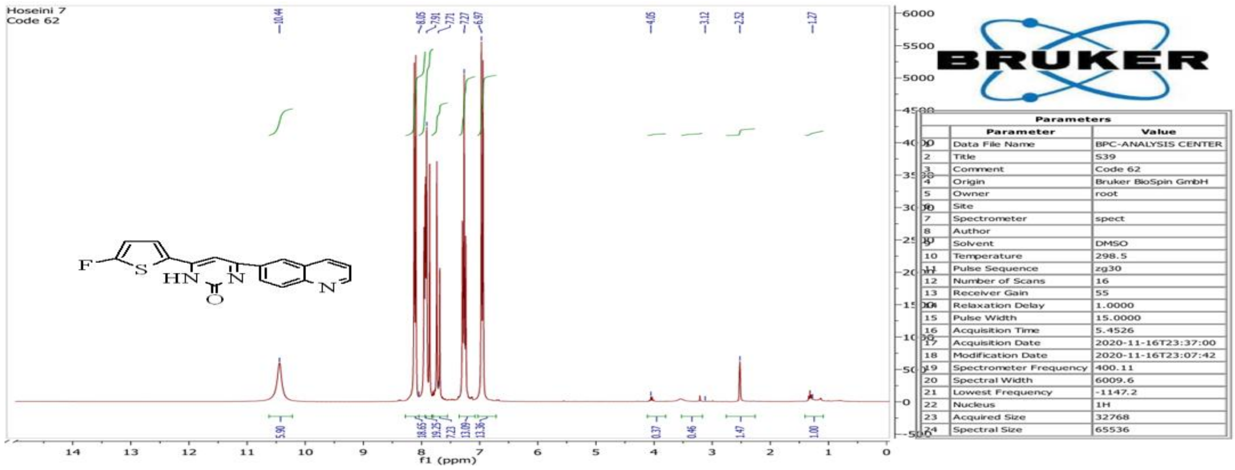


Fig.5 1H-NMR of W2

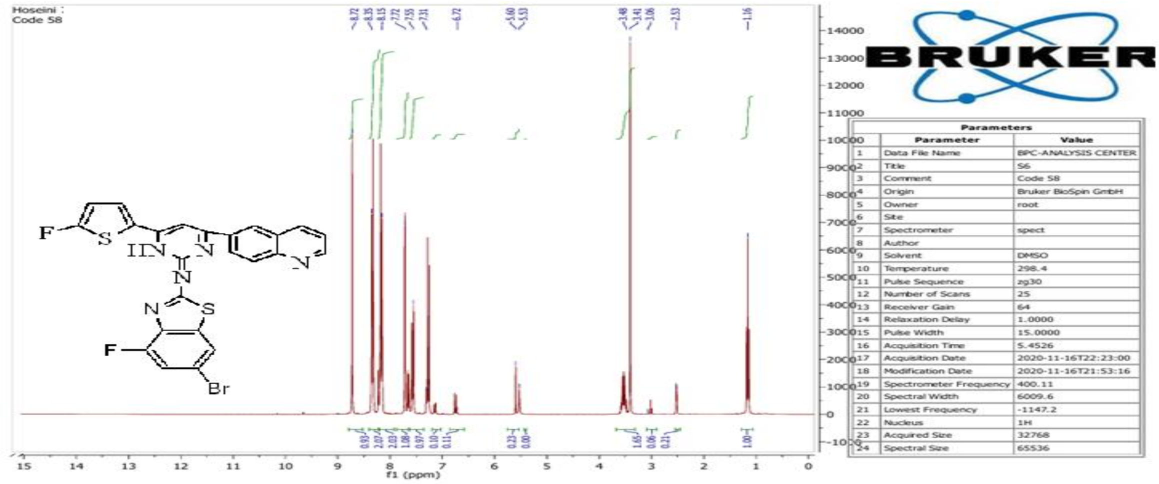


Fig.6 1H-NMR of W6

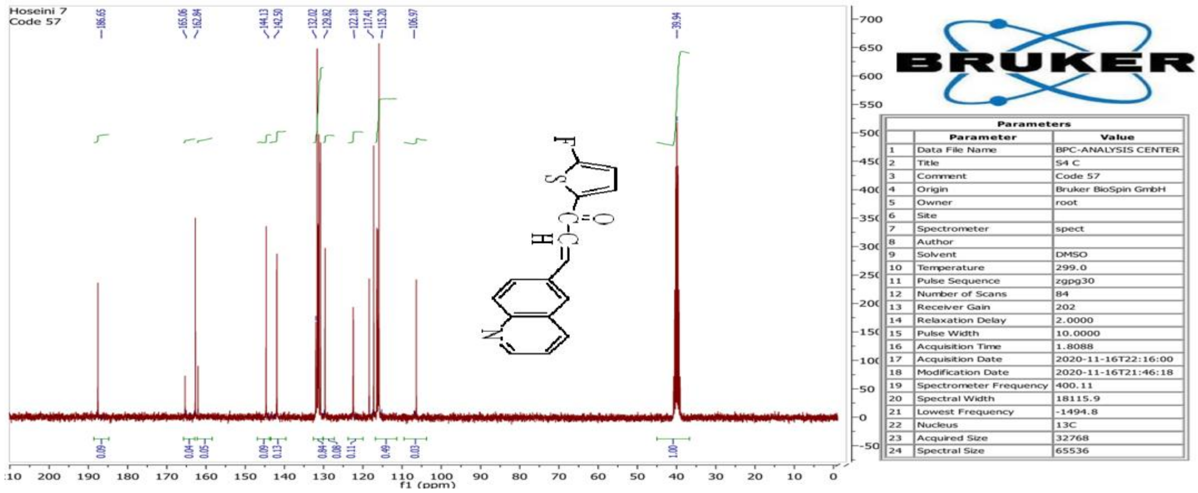


Fig.7 ^{13}C-NMR of W1

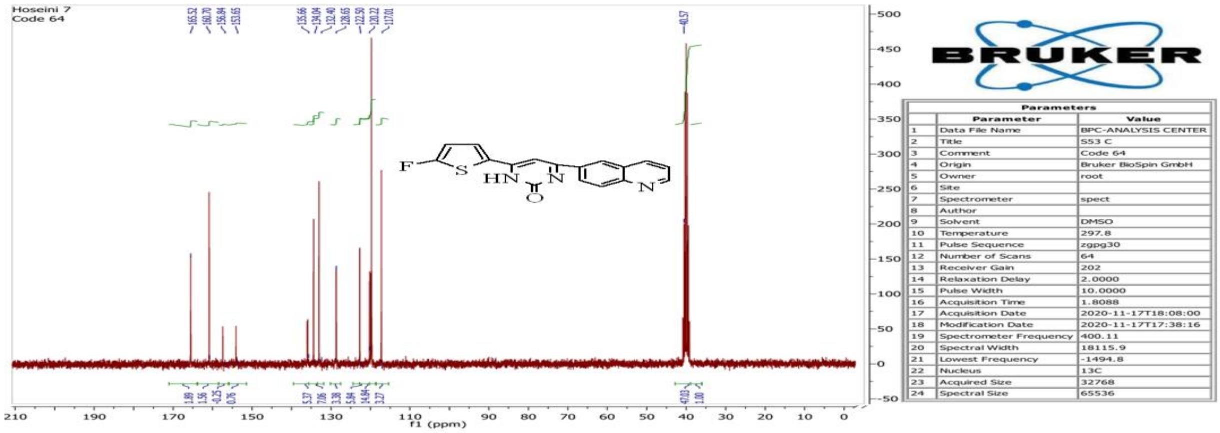


Fig.8 ^{13}C-NMR of W2

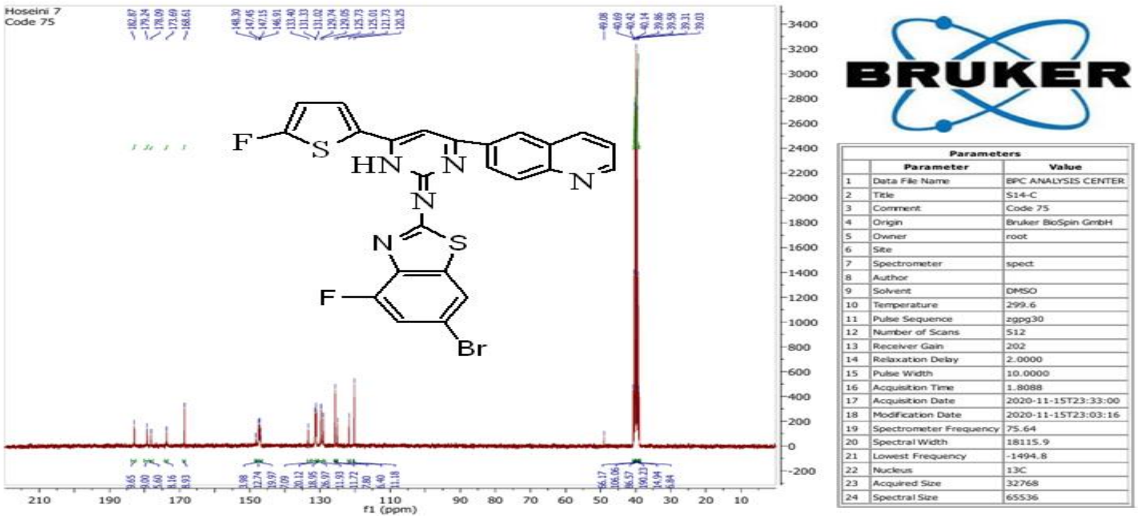


Fig.9 [13]C-NMR of W6

Table 4 .Antioxidant activities of compounds W1-,W2,W3,W6,W9,W10 in terms of their IC50 and half-maximal inhibitory concentration

Symbol of compounds	Concentration (ppm)	I%	IC50 (mg/mL
	50	19.86	
W1	100	20.33	
	150	25.66	6.9
	200	40.58	
	250	40.56	
	50	29.16	
	100	31.66	
W2	150	35.95	5.6
	200	36.28	
	250	40.86	
	50	8.4	
	100	23.55	
W3	150	31.12	6.4
	200	35.55	
	250	43.18	
	50	33.61	
	100	34.72	
W6	150	35.83	6.8
	200	37.77	
	250	39.58	
	50	39	
	100	51	
W9	150	77	3.2
	200	78	
	250	81	
	50	40.69	
W10	100	45.94	
	150	51.8	3.7
	200	66.11	
	250	80.21	

4. Conclusion

The compounds of pyrimidine, thiazolidine, and substituted 2-aminobenzothazol have been effectively synthesized with yields ranging from 41 to 61%. FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy were used to verify the produced compounds. The antioxidant properties of a few of the produced substances were tested. The results demonstrate the synthesized compounds' potential as worthwhile candidates for additional investigation in the field of antioxidant research.

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